

**IS WEANING FAILURE CAUSED BY LOW-FREQUENCY FATIGUE OF THE
DIAPHRAGM?**

Running Head: Diaphragmatic fatigue in weaning

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ABSTRACT

Because patients who fail a trial of weaning from mechanical ventilation experience a marked increase in respiratory load, we hypothesized that these patients develop diaphragmatic fatigue. Accordingly, we measured twitch transdiaphragmatic pressure using phrenic nerve stimulation in 11 weaning failure and 8 weaning success patients. Measurements were made before and 30 minutes after spontaneous breathing trials that lasted up to 60 minutes. Twitch transdiaphragmatic pressure was 8.9 ± 2.2 cm H₂O before the trials and 9.4 ± 2.4 cm H₂O after their completion in the weaning failure patients ($p=0.17$); the corresponding values in the weaning success patients were 10.3 ± 1.5 cm H₂O and 11.2 ± 1.8 cm H₂O ($p=0.18$). Despite greater load ($p=0.04$) and diaphragmatic effort ($p=0.01$), the weaning failure patients did not develop low-frequency fatigue probably because of greater recruitment of rib-cage and expiratory muscles ($p=0.004$) and because clinical signs of distress mandating the reinstatement of mechanical ventilation arose before the development of fatigue. Twitch pressure revealed considerable diaphragmatic weakness in many weaning failure patients. In conclusion, contrary to our hypothesis, weaning failure was not accompanied by low-frequency fatigue of the diaphragm although many weaning failure patients displayed diaphragmatic weakness.

Word count = 192

Key words: ventilator weaning, respiratory muscles, muscle fatigue, phrenic nerve, respiratory insufficiency.

INTRODUCTION

When a mechanical load on the respiratory system is too large or continues for too long a time, the respiratory muscles can develop contractile fatigue (1). In the context of neurophysiology, fatigue represents a decrease in muscle force in response to a given neural stimulus. Contractile fatigue can be short-lasting or long-lasting. Short-lasting fatigue, also known as high-frequency fatigue, results from accumulation of inorganic phosphate (2), failure of the membrane electrical potential to propagate beyond T-tubes (3), and to a lesser extent intramuscular acidosis (4). Long-lasting fatigue (5), also known as low-frequency fatigue, is consistent with the development of, and recovery from, muscle injury (6,7) and it can persist for days. Contractile fatigue can be induced in healthy subjects under constrained experimental conditions when subjects willingly continue to generate large subatmospheric swings in intrathoracic pressure irrespective of afferent signals from the respiratory muscles or elsewhere (5,8,9).

Patients who fail a trial of weaning from mechanical ventilation are at considerable risk for developing respiratory muscle fatigue. Much circumstantial evidence suggests that these patients do develop contractile fatigue (10-15). For example, we found that 5 of 17 weaning failure patients experienced an imbalance between mechanical load and respiratory muscle capacity, expressed as tension-time index, which would be expected to induce contractile muscle fatigue (13). None of the experimental techniques used to date, however, provides direct evidence of contractile fatigue, and it is still unknown whether or not contractile fatigue occurs in patients.

The question of whether respiratory muscle fatigue occurs in weaning failure patients is of major clinical importance. Patients who fail a trial of weaning are at a disadvantage when compared with weaning success patients because they have greater abnormalities in lung mechanics (13-15). If these patients also develop contractile fatigue of their respiratory muscles during a failed weaning trial, the superimposed structural injury is likely to set them back in their clinical course. The new injury might even become the ultimate determinant of whether or not some patients are ever successfully weaned from the ventilator.

The most direct method for detecting fatigue in patients is to stimulate the phrenic nerves and measure the resulting change in transdiaphragmatic pressure. We used this approach to test the hypothesis that patients who fail a trial of weaning from the mechanical ventilation develop contractile fatigue of the diaphragm whereas successfully weaned patients do not. Some the results of these studies have been previously reported in the form of abstracts (16,17).

METHODS (word count = 553)

Patients

Nineteen patients whose primary physician considered them ready for weaning were recruited (Table 1) (further details are available in the online data supplement). Appropriate institutional review boards approved the study and written consents were obtained.

Experimental setup

Flow and pressure measurements. Flow and airway, esophageal (Pes), gastric (Pga) and transdiaphragmatic (Pdi) pressures were measured. (Further details are available in online data supplement.)

Compound diaphragmatic action potentials. Compound diaphragmatic action potentials (CDAPs) were recorded bilaterally using surface electrodes. Single bilateral phrenic nerve stimulation was performed using two magnetic stimulators with two sets of double 40-mm coils that generated a magnetic field of 3.2 Tesla at maximal output. (Further details are available in online data supplement.)

Protocol

Twitch stimulation before the weaning trial. To avoid twitch potentiation (5,18), the patients received controlled ventilation for 20 minutes before delivering the first stimulation. Six to 15 stimulations were then delivered bilaterally at intervals of about 15 seconds at end-exhalation while closing the in-line valve. After the last stimulation, maximal voluntary inspiratory efforts were recorded during a 20-second occlusion of the airway (19) (see online data supplement for details).

Trial of spontaneous breathing. The weaning trial was conducted for up to one hour as tolerated. In eight weaning failure and in four weaning success patients, arterial blood samples were obtained at 2 minutes and at the end of the trial. Patients who did not

develop criteria of weaning failure (13,20) (criteria listed in online data supplement) were extubated. Patients who sustained spontaneous breathing for more than 24 hours were deemed the weaning successes group (21). The remaining patients, the weaning failure group, required mechanical ventilation for 3 days to more than 57 days after the study.

Twitch stimulation after the trial. After the weaning trial, all patients irrespective of the weaning outcome, were returned to mechanical ventilation for 30 minutes. At the end of this period, twitch Pdi and maximal voluntary inspiratory efforts were measured. To determine whether maximal depolarization of the phrenic nerve was achieved, progressively increasing outputs from the stimulator were delivered in 12 patients (see online data supplement for details). Thereafter, patients who had met the a priori criteria of weaning failure were maintained on mechanical ventilation whereas the remaining patients were extubated.

Twitch interpolation: Twitch interpolation measurements were performed in seven patients before and after the weaning trial (22) (see online data supplement for details).

Physiologic measurements

Transdiaphragmatic twitch pressure. Twitch Pdi was measured as the difference between the maximum Pdi displacement secondary to phrenic nerve stimulation and the value immediately before stimulation (18,23). Criteria for acceptable twitch responses are listed in the online data supplement. The within-occasion coefficient of variation of twitch Pdi before and after weaning was 10% or less in 17 patients and it was within 12

and 14% in the remaining two patients. Data collected after the weaning trial did not satisfy the a priori criteria for acceptable twitch responses in 3 of the 19 patients, and they were excluded from data analysis.

Maximum voluntary inspiratory pressure. The pressure developed by the diaphragm was computed as the maximal excursion in Pdi (Pdimax) during the 20-second occlusions (19).

Respiratory mechanics and effort indices. Inspiratory resistance of the lung, dynamic compliance of the lung, and intrinsic positive end-expiratory pressure (PEEPi) were computed according to standard formulae (24-27). Pressure-time product (PTPdi) and tension-time index (TTdi) of the diaphragm were quantified using standard formulae (1,26-28). The relative contribution of the different respiratory muscles to tidal breathing was assessed as the ratio of swings in Pga to swings in Pes ($\Delta P_{ga}/\Delta P_{es}$). (See online data supplement for calculation of these variables.)

Data Analysis

Analysis of variance and t-tests were used as needed (see online data supplement). Some measurements are included in another manuscript (29).

RESULTS

Nine patients met the a priori criteria for weaning failure after 44 ± 7 minutes of spontaneous breathing and mechanical ventilation was reinstated. Seven patients tolerated a trial of 60 minutes without distress and were extubated.

At the beginning of the weaning trial, PaO₂, PaCO₂, and pH were not different between the groups (Table 2). By the end of the trial, a small decrease in pH ($p = 0.025$) occurred in the failure group and no significant change occurred in the success group.

Twitch and maximal inspiratory pressures

Magnetic stimulation elicited twitch pressures in all patients (Figure 1). Before the weaning trial, twitch Pdi was 8.9 ± 2.2 cm H₂O in the failure group and 10.3 ± 1.5 cm H₂O in the success group ($p = 0.63$) (Figure 2). After the trial, twitch Pdi was 9.4 ± 2.4 in the failure group and 11.2 ± 1.8 cm H₂O in the success group ($p = 0.58$); these values were not different from the values for each group before the trial. (In the failure patient who had a malfunctioning gastric balloon, twitch Pes was -20.6 ± 0.6 cm H₂O before and -18.2 ± 0.6 cm H₂O after the trial.) Before the trial, Pdimax was 39.4 ± 6.6 cm H₂O in the failure group and 55.2 ± 8.2 cm H₂O in the success group ($p = 0.36$) (Figure 3). The values of Pdimax at 30 minutes after the trial were 41.0 ± 6.8 cm H₂O in the failure group and 53.5 ± 8.3 cm H₂O in the success group ($p = 0.26$); these values were not different from the values for each group before the trial.

Among the seven patients in whom twitch interpolation was performed, the amplitude of the diaphragmatic CDAP during interpolation was less than that during

passive conditions. A detectable superimposed twitch, however, was always present -- even in those four patients in whom it was possible to time the superimposed stimulus at, or near to, Pdimax (Figure 4). This observation suggests that the phrenic nerve was not maximally stimulated by a “maximal” voluntary maneuver.

Diaphragmatic pressure output (PTPdi) and tension time index (TTdi)

At trial onset, PTPdi/min was 337 ± 51 cm H₂O*second/minute in the failure group and 205 ± 27 cm H₂O*second/minute in the success group (Figure 5). At the end of the trial, PTPdi/min increased to 523 ± 130 cm H₂O*second/minute in the failure group ($p < 0.05$) and to 367 ± 64 cm H₂O*second/min in the success group ($p < 0.01$). Over the course of the trial, PTPdi/min did not differ between the two groups ($p = 0.18$).

Over the course of the trial, TTdi was higher in the failure group than in the success group ($p = 0.01$) (Figure 5). Of the 9 failure patients, 7 had a TTdi at or above 0.15 (the putative threshold for task failure and fatigue) during two or more isotimes. Of the 7 success patients, only 1 had a TTdi at or above 0.15 during two isotimes.

Rib-cage and expiratory muscle recruitment

At trial onset, $\Delta P_{ga}/\Delta P_{es}$ ratio was greater in the failure group than in the success group: -0.03 ± 0.04 versus -0.19 ± 0.05 ($p = 0.002$) (Figure 6). Over the course of the trial, $\Delta P_{ga}/\Delta P_{es}$ remained greater in weaning failure patients ($p = 0.004$). At the end of the trial, the ratio had increased to 0.12 ± 0.07 in the failure group ($p = 0.05$). At the end of the trial, the ratio in the success group was -0.10 ± 0.02 . Because patients with diaphragmatic

paralysis can have enhanced rib-cage muscle recruitment even in the absence of respiratory distress (30), $\Delta P_{ga}/\Delta P_{es}$ ratio of the failure patients was compared with that of the success patients after excluding the two patients (both weaning failure patients) with hemidiaphragmatic paralysis. The $\Delta P_{ga}/\Delta P_{es}$ was still greater in the weaning failure patients ($p = 0.01$) -- a finding similar to the overall group.

Respiratory mechanics

At onset of the trial, inspiratory resistance of the lung was not different between the failure and success groups: 12.8 ± 1.8 versus 10.4 ± 0.6 cm H₂O/liter/second ($p=0.44$). During the course of the trial, inspiratory resistance of the lung in the failure group became greater than in the success group ($p= 0.05$) (data not shown). At trial onset, dynamic compliance of the lung was 55 ± 11 ml/cm H₂O in the failure group and 184 ± 81 ml/cm H₂O in the success group. During the course of the trial, dynamic lung compliance was lower in the failure group than that in the success group ($p=0.042$) (data not shown).

At onset of the trial, total PEEP_i (not corrected for expiratory rise in P_{ga}) was not different between the failure and success groups: 4.6 ± 1.3 versus 2.1 ± 0.4 cm H₂O and ($p = 0.13$). Likewise, corrected PEEP_i (corrected for expiratory rise in P_{ga}) was not different between the failure and success groups: 3.8 ± 1.2 versus 2.1 ± 0.4 cm H₂O ($p = 0.59$). At the end of the trial, total PEEP_i had increased to 11.6 ± 4.4 cm H₂O ($p = 0.03$) in the failure group and to 4.4 ± 1.0 cm H₂O ($p = 0.001$) in the success group. At

the end of the trial, corrected PEEP_i was 6.2 ± 3.6 cm H₂O in the failure group. The values of total and corrected PEEP_i in the success patients were nearly identical.

DISCUSSION

This is the first report of systematic measurements of the contractile response of the diaphragm to phrenic nerve stimulation in patients being weaned from mechanical ventilation. We found that patients failing a weaning trial did not develop low-frequency fatigue.

Researchers have long thought that some, if not most, patients who fail a weaning trial develop respiratory muscle fatigue (10,12-15). The techniques used in previous studies were indirect (10-14), raising doubt as to whether fatigue truly occurred (31). We used a direct test of muscle fatigability, namely stimulation of the phrenic nerve and measurement of the resulting P_{di} (32,33). Even with this technique, data can be inaccurate because of several confounding variables: changes in lung volume, variation in the degree of neural depolarization achieved by the stimulator, and the contraction history of the muscle (i.e., twitch potentiation). We took particular care to avoid these confounding factors, and excluded data that did not satisfy our a priori inclusion criteria. As such, we view the absence of a fall in twitch P_{di} as evidence that low-frequency fatigue is not a mechanism of weaning failure.

Factors that can contribute to fatigue

Diaphragmatic fatigue occurs only when there is a critical stress on the muscle. A critical stress can result from an increase in mechanical load, which leads to an increase in respiratory center output and thus increase in respiratory muscle pressure (PTPdi). When a patient's muscle strength is small, an increase in PTPdi is more likely to exceed the diaphragmatic threshold (TTdi) for fatigue (1).

At onset of the weaning trial, the weaning failure patients had abnormalities in lung mechanics comparable to those reported in previous studies: inspiratory resistance of the lung was 13 cm H₂O/liter/second versus 9 (13) and 22 cm H₂O/liter/second (14); dynamic lung compliance was 55 ml/cm H₂O versus 48 (13) and 70 ml/cm H₂O (14); and total PEEPi was 4.6 cm H₂O versus 2.0 (13) and 5.9 cm H₂O (14). By the end of the trial, inspiratory resistance of the lung (17 cm H₂O/liter/second) and total PEEPi (12 cm H₂O) increased to, or exceeded, previously reported values (16 cm H₂O/liter/second and 4 cm H₂O, respectively (13)). Dynamic lung compliance at the end of a failed trial was within the range of previously reported values: 48 ml/cm H₂O versus 29 (13) and about 70 ml/cm H₂O (14). Accordingly, our weaning failure patients displayed abnormalities in pulmonary mechanics equivalent to patients in previous studies. Our weaning failure patients displayed greater resistive and elastic loads than did our weaning success patients – a finding similar to our previous report (13).

The increase in PTPdi over the course of the weaning trial indicates that the respiratory centers attempted to defend alveolar ventilation in the face of deteriorating lung mechanics. This finding is consistent with our previous report of an increase in

overall respiratory muscle pressure (PTPes) (13). In that previous study (13), the increase in PTPes was not sufficient to prevent hypercapnia in 13 of the 17 weaning failure patients. Hypercapnia was less common in the present study: PaCO₂ increased by 5 to 16 mm Hg in three of eight weaning failure patients in whom arterial blood samples were obtained. Three factors may account for the difference in the two studies: baseline arterial samples were collected at about 2 minutes after the start of spontaneous breathing in the present study whereas they were collected during controlled mechanical ventilation in the previous study; only four weaning failure patients in the present study had COPD as compared with all patients in the previous study; and respiratory muscle effort, as reflected by PTPes, was somewhat greater in the present study than in the previous study (538 and 388 cm H₂O*s/minute, respectively).

Tension-time index (TTdi) combines three key determinants of diaphragmatic fatigue: pressure generated by the diaphragm (PTPdi), muscle strength (Pdimax), and respiratory duty cycle (T_I/T_{TOT}). In healthy subjects, a sustained increase in TTdi above 0.15 leads to diaphragmatic fatigue (1). The threshold of 0.15 was exceeded by 77% of our weaning failure patients and by 15% of our weaning success patients. Yet, no patient showed evidence of low-frequency fatigue. Three factors could explain why a high TTdi was not accompanied by fatigue: the heightened muscle effort was not sustained for a sufficient time; endurance of the diaphragm was greater in weaning failure patients than in healthy subjects; and the recorded value of TTdi was an overestimate.

Bellemare and Grassino (1) reported that the relationship between TTdi and time to task failure in healthy subjects follows an inverse power function: time to task failure = $0.1 (\text{TTdi})^{-3.6}$. The average duration of weaning trials in our failure patients was 44 minutes. The average values of TTdi for the first, second, third, and fourth quintiles of the trial durations were 0.17, 0.17, 0.22, and 0.22, respectively. Based on the formula of Bellemare and Grassino (1), the expected times to task failure for the respective quintiles would be 59, 59, 28, and 28 minutes. The average value of TTdi during the last minute of the trial was 0.26, and the weaning failure patients would be predicted to sustain this effort for another 13 minutes before developing task failure. These calculations suggest that weaning failure patients did not sustain the increase in load for a duration sufficient to cause low-frequency fatigue; that is, the trial was stopped because patients developed a priori-defined clinical manifestations of respiratory distress before they developed fatigue.

Fatigue is not an all-or-none phenomenon (34). Measuring twitch pressures after forceful voluntary contractions, so-called potentiated twitches, has been suggested as a means for detecting an early decrease in muscle contractility (34,35). In eight patients (four weaning failure and four weaning success patients), we were able to record the potentiated twitches both before and after weaning by stimulating the phrenic nerves immediately after the patients performed maximal voluntary inspiratory efforts. Potentiated twitch Pdi was 8.6 ± 3.1 cm H₂O before the trial and 8.7 ± 2.9 cm H₂O after the trial in the four weaning failure patients; the corresponding values for non-potentiated twitches were 6.9 ± 2.6 and 6.8 ± 2.4 cm H₂O, respectively. Potentiated

twitch Pdi was 10.5 ± 1.5 cm H₂O before the trial and 10.6 ± 1.1 cm H₂O after the trial in the four weaning success patients; the corresponding values for non-potentiated twitches were 8.3 ± 1.5 and 8.7 ± 1.4 cm H₂O, respectively. The failure of potentiated twitch Pdi to decrease after a failed weaning trial further supports our reasoning that the inspiratory load, even if it was in the fatiguing range, was not sustained for a sufficient length of time to cause fatigue.

If endurance of the respiratory muscles is supranormal in critically ill patients, fatigue would not develop at a TTdi of 0.15. Direct measurements of diaphragmatic endurance have not been obtained in critically ill patients, but circumstantial evidence suggests that it is not supranormal. Indeed, endurance of the diaphragm is decreased in stable patients with spinal cord injury (36), probably because fatigue-sensitive, Type II myosin heavy chains are increased in the diaphragm (37).

Reliable calculation of TTdi is critically dependant on an accurate measurement of diaphragmatic strength. Our data show that even carefully made measurements of Pdimax commonly underestimate maximum strength. The pressure tracings in all of our patients during the Pdimax measurements had the characteristics of a Mueller maneuver: large negative excursions in Paw and Pes with slightly positive (or, in one patient, negative) deflections in Pga (Figure 4). In healthy subjects, the combination of a Mueller maneuver with an expulsive maneuver results in higher values of Pdimax (38), but critically ill patients have great difficulty in performing the combined maneuver. Moreover, the finding of twitch interpolation (that is, a measurable twitch Pdi when the

phrenic nerves were stimulated during maximum voluntary effort) indicates that patients were not able to completely activate the diaphragm during a “maximum” maneuver (22) (Figure 4). The underestimation of P_{dimax} will necessarily produce an overestimate of TT_{di} , which further explains why patients did not develop low-frequency fatigue despite recorded values of TT_{di} above 0.15.

Defense mechanisms against low-frequency fatigue

All of the weaning failure patients experienced severe respiratory distress, yet none developed low-frequency fatigue. Three strategies may have protected the diaphragm against fatigue: increased rib-cage and expiratory muscle recruitment, the early reinstatement of mechanical ventilation, and respiratory center downregulation.

Immediately after the start of the weaning trial, the weaning failure patients displayed greater recruitment of rib-cage and expiratory muscles during tidal breathing than did the weaning success patients (greater $\Delta P_{ga}/\Delta P_{es}$)(Figure 6). (Excluding the two patients with hemidiaphragmatic paralysis does not affect this finding.) The same alteration in respiratory muscle recruitment has also been reported in patients (39-42) and volunteers (34,43) when diaphragmatic effort is increased during tidal breathing. Recruitment of the rib-cage and expiratory muscles appears to contribute to the development of dyspnea (41,44). Clinicians also take increased activity of the rib-cage and abdominal muscles into account in deciding whether to continue or interrupt a weaning trial.

The increase in PTPdi during the weaning trial signifies a progressive increase in respiratory motor output, as has been previously reported (14,45,46). Some patients, however, developed hypercapnia, suggesting that respiratory motor output may have been downregulated. Studies in animals show that a decrease in respiratory motor output occurs as a preterminal event (47), and decrease in drive can be accompanied by the development of diaphragmatic fatigue at the time of apnea (48). Afferent signals originating in fatiguing muscles may activate neural pathways responsible for downregulation of respiratory motor output (49-52). Downregulation of respiratory drive will decrease metabolic demands and the likelihood of contractile fatigue (53). During the usual protocol for inducing respiratory muscle fatigue in healthy volunteers (achieving a target inspiratory pressure while breathing through a resistor (1,5,9)), the exhortation of the investigators and the volition of the subjects may override the afferent signals that downregulate respiratory drive (9). The artificial and constrained nature of this laboratory protocol is very different from the natural evolution of respiratory distress in weaning failure patients.

Other causes of weaning failure

Although low-frequency fatigue does not appear to be responsible for weaning failure, other abnormalities of the respiratory muscles may be causative. Possible mechanisms include diaphragmatic weakness, atrophy, high-frequency fatigue, and hyperinflation.

In our laboratory, the mean amplitude of non-potentiated twitch Pdi ranges from 35.4 to 38.9 cm H₂O in healthy subjects (5,23,34) and from 17.2 to 20.1 cm H₂O in stable patients with COPD (54,41). Most of our weaning failure and weaning success patients had twitch Pdi values lower than the values recorded in ambulatory patients. Six weaning failure patients had twitch Pdi values of less than 10 cm H₂O. These results suggest that many mechanically ventilated patients have diaphragmatic weakness and that some weaning failure patients have severe weakness.

Eight weaning failure patients and six weaning success patients had infections (pneumonia or sepsis) while receiving ventilator support. Sepsis is known to cause diaphragmatic injury and weakness (55,56). All of our patients had been ventilated with patient-triggered modes, and the involved muscle contractions may aggravate the diaphragmatic injury caused by sepsis (57). Several studies in experimental animals (58) demonstrate that mechanical ventilation can induce respiratory muscle atrophy, although it is not known whether this occurs in patients. Many ventilator-supported patients are malnourished (59) and this will further contribute to atrophy (60-62).

Our study does not directly address whether or not the patients developed high-frequency fatigue, as has been suggested (11). The lack of change in twitch Pdi and Pdimax does not exclude the possibility. High-frequency fatigue can resolve within 10 to 15 minutes (4,53), and it could have disappeared by the time of testing (30 minutes after the end of the weaning trial).

Weakness of the inspiratory muscles arises when patients develop progressive hyperinflation. An increase in end-expiratory volume causes shortening of inspiratory muscles and a decrease in force generation. Total PEEP_i increased over the course of the trial in the weaning failure patients, but an indirect measurement of end-expiratory volume -- PEEP_i corrected for expiratory muscle recruitment (26) -- revealed no change. Corrected PEEP_i was also not different between weaning success and weaning failure patients, suggesting that hyperinflation did not increase during the trials.

Clinical Implications

Respiratory muscle fatigue has been thought to be a common cause of weaning failure, and accordingly clinical management has been directed towards improving the capacity of the respiratory muscles to generate (strength) and to sustain (endurance) force (63). Does the lack of low-frequency fatigue in our weaning failure patients mean that these strategies are misdirected? No. Many weaning failure patients have severe diaphragmatic weakness (66% had twitch P_{di} values below 10 cm H₂O), and weakness probably sets in motion the complex processes described in this study, which ultimately lead to the early reinstatement of mechanical ventilation.

Investigators have shown that respiratory muscle training can increase respiratory muscle strength and endurance in ambulatory patients, but the improvement has not been shown to achieve better clinical well being or outcome (64,65). The lack of benefit is not surprising because baseline maximum inspiratory pressure was not reduced to a level that hinders spontaneous breathing (66). In weaning failure patients,

however, a small improvement in respiratory muscle strength and endurance could have a profound effect on clinical outcome. Based on the results of the present study, it could prove useful to develop a training regimen that can achieve an improvement in twitch pressure (the non-invasive measurement of twitch airway pressure may satisfactorily substitute for twitch Pdi (29)). Such a training regimen could have a major benefit in the difficult-to-wean patients (63), although proof of this possibility requires a randomized control trial. While the challenge of designing and undertaking such a trial will be considerable, the scientific motivation for such a study is stronger than before.

In summary, patients who fail a weaning trial displayed greater mechanical load than did weaning success patients. The increase in load caused TTdi to increase above the threshold associated with fatigue, yet twitch Pdi and Pdimax did not decrease in these patients. Factors that may have protected the diaphragm against fatigue include greater rib-cage and expiratory muscle recruitment, downregulation of respiratory motor output, and early reinstatement of mechanical ventilation. In conclusion, contrary to our hypothesis, weaning failure was not accompanied by low-frequency fatigue of the diaphragm although many weaning failure patients displayed severe diaphragmatic weakness.

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Figure 1. Esophageal pressure (Pes), gastric pressure (Pga), transdiaphragmatic pressure (Pdi), and compound motor action potentials (CAMP) of the right and left hemidiaphragms following phrenic nerve stimulation before (left) and after (right) a failed trial of weaning. The end-expiratory value of Pes and the amplitude of the right and left CAMPs were the same before and after the trial, indicating that the stimulations were delivered at the same lung volume and that the stimulations achieved the same extent of diaphragmatic recruitment. The amplitude of twitch Pdi elicited by phrenic nerve stimulation was the same before and after weaning.

Figure 2. Transdiaphragmatic twitch pressure (twitch Pdi), recorded before and 30 minutes after a weaning trial, in 9 weaning failure patients (left panel) and 7 weaning success patients (right panel). Twitch Pdi did not differ between the groups before the trial, and it did not decrease after the trial in either group. Values are mean \pm SE

Figure 3. Maximum transdiaphragmatic pressure (Pdimax), recorded before and 30 minutes after a weaning trial, in 9 weaning failure patients (left panel) and 7 weaning success patients (right panel). Pdimax did not differ between the groups before the trial, and it did not decrease after the trial in either group. Values are mean \pm SE.

Figure 4. Continuous recordings of esophageal pressure (Pes), gastric pressure (Pga), and transdiaphragmatic pressure (Pdi) during airway occlusion in a patient after a failed trial of weaning. Phrenic nerve stimulation (arrow) during the maximal inspiratory effort resulted in a detectable superimposed twitch. The presence of a superimposed twitch during a maximal effort indicates that voluntary activation of the diaphragm was incomplete.

Figure 5. Pressure-time product (PTPdi) (left) and tension-time index of the diaphragm (TTdi) (right) during a weaning trial in the failure (closed symbols) and success (open symbols) groups. Between the onset and the end of the trial, increases in PTPdi ($p < 0.005$) and TTdi ($p < 0.005$) occurred in both groups. Over the course of the trial, the failure group had higher values of TTdi ($p = 0.01$) but not of PTPdi ($p = 0.18$) than did the success group. Bars represent \pm SE.

Figure 6. Ratio of inspiratory change in gastric pressure to esophageal pressure ($\Delta P_{ga}/\Delta P_{es}$) – an index of rib-cage and expiratory muscle contribution to respiratory effort – during a weaning trial in the failure (closed symbol) and success (open symbol) groups. Between the onset and the end of the trial, $\Delta P_{ga}/\Delta P_{es}$ increased in the failure ($p = 0.04$) and success groups ($p = 0.05$), and the ratio was higher in the failure group than in the success group over the course of the trial ($p = 0.004$). Bars represent \pm SE.

Table 1.

Weaning Success

Patient No.	Age (yr)	Sex	Diagnosis	ETT (ID mm)	Trach (ID mm)	Days of ventilator support
1	81	M	Subdural hematoma, aspiration pneumonia, COPD	7.5		5
2	48	M	Postoperative sepsis, acute renal failure		8	29
3	64	M	Pneumonia, alveolar hemorrhage, C ₅₋₆ quadriplegia, COPD		8	8
4	61	M	Myocardial infarction, coronary artery graft, pneumonia, COPD		6	25
5	70	M	Pneumonia, gastrointestinal bleed, myocardial infarction	8		13
6	43	F	Cocaine-induced bronchospasm	7.5		2
7	75	M	Heart failure, cardiac arrest*	7.5		5
8	78	M	Sepsis, pancreatitis, myocardial infarction	8		5

Weaning failure

Patient No.	Age (yr)	Sex	Diagnosis	ETT (ID mm)	Trach (ID mm)	Days of ventilator support
1	84	M	Myocardial infarction, pneumonia		6	22
2	64	M	Cardiac arrest, cardiogenic shock	8		17
3	78	M	Sepsis, coronary artery graft, gastrointestinal bleed, left diaphragmatic paralysis		6	68
4	81	M	Pneumonia, myocardial infarction, coronary artery graft, right diaphragmatic parlays		8	53
5	50	M	Pulmonary embolus, COPD	8		8
6	45	M	Sepsis, demyelinating polyneuropathy	8		16
7	54	M	Postoperative sepsis, renal failure, COPD	8		12
8	70	M	Pneumonia, ARDS, COPD		6	26
9	75	M	Pneumonia, stroke, COPD*	8		12
10	22	M	C ₄₋₅ quadriplegia*		7	190
11	57	M	Pneumonia, COPD exacerbation		6	33

* = patients excluded from data analysis because twitch responses did not satisfy the a priori criteria for acceptability.

ETT = endotracheal tube; trach = tracheostomy tube; ID mm = internal diameter in millimeters; ARDS = Acute respiratory distress syndrome.

Table 2

Alterations in Arterial Blood Gas Measurements

	PaO ₂		PaCO ₂		pH	
	(mm Hg)		(mm Hg)			
	Start	End	Start	End	Start	End
Weaning failure	88 ± 4	83 ± 6	45 ± 3	47 ± 4	7.38 ± .02	7.36 ± .02 *
Weaning success	90 ± 9	93 ± 6	42 ± 6	43 ± 6	7.39 ± .04	7.38 ± .04

The fractional inspired oxygen concentration was 0.40 in all instances.

Start = spontaneous breathing at start of trial; End = spontaneous breathing at end of trial

Values are mean ± SE

* p = 0.025, difference between start and end of trial of spontaneous breathing

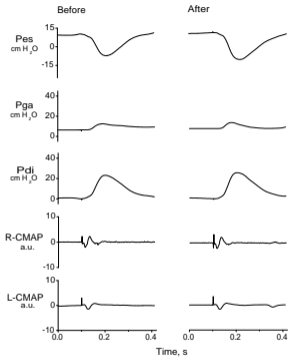


Figure 1

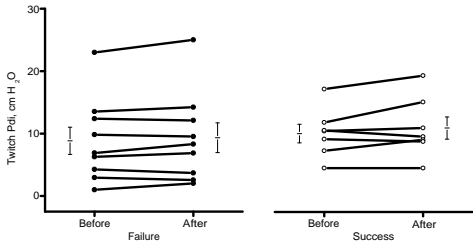


Figure 2

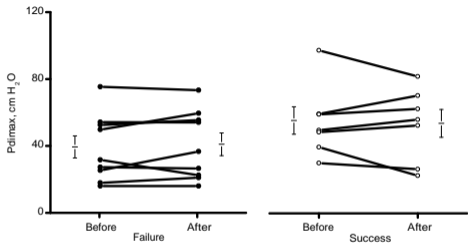


Figure 3

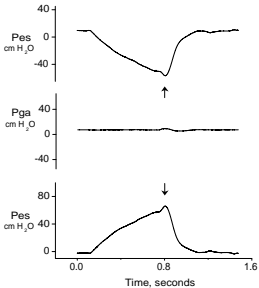


Figure 4

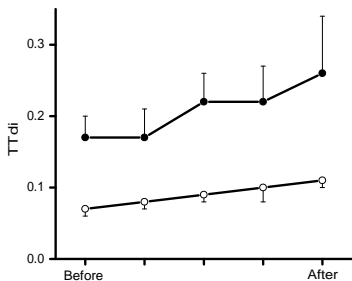
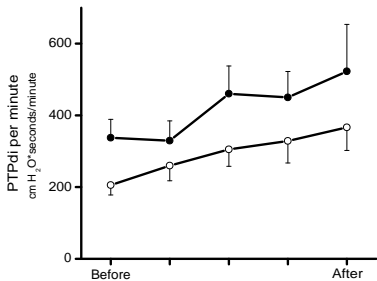


Figure 5

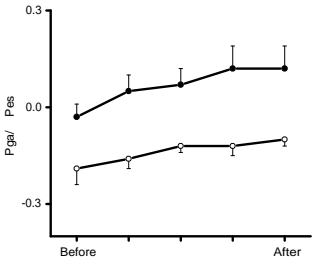


Figure 6

***SUPPLEMENTARY MATERIAL FOR
ON-LINE ONLY REPOSITORY***

**IS WEANING FAILURE CAUSED BY LOW-FREQUENCY FATIGUE OF THE
DIAPHRAGM?**

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Word Count: 1651

METHODS

Patients

Nineteen clinically stable patients who had required mechanical ventilation for at least 48 hours because of an episode of respiratory failure were studied. Patients were ventilated in the assist-control mode using a Puritan-Bennett 7200a ventilator through a cuffed endotracheal (n = 10) or tracheostomy tube (n = 9). No patient with a cardiac pacemaker was enrolled, and no patient had received neuromuscular blocking agents within the two days preceding the study.

Experimental Setup

Flow and pressure measurements. Esophageal pressure (Pes) and gastric pressure (Pga) were separately measured with two thin-walled, balloon-tipped catheters coupled to pressure transducers. Proper positioning of the esophageal balloon was ensured with the occlusion technique (1). Transdiaphragmatic pressure (Pdi) was obtained by subtracting Pes from Pga. Airway pressure was measured at the external end of the endotracheal or tracheostomy tube with a side port connected to a pressure transducer. Just distal to this side port, flow was continuously measured with a heated pneumotachograph (Hans Rudolph, Kansas City, MO). Between the pneumotachograph and the Y-piece of the ventilator, an in-line valve allowed for intermittent airway occlusion.

Compound diaphragmatic action potentials. Surface electrodes were placed at the level of the 7th and 8th intercostal space and the anterior axillary line to measure

compound diaphragmatic action potentials (CDAPs). Noise-to-signal ratio was decreased by tying excess electromyography cable into a coil, and by testing the optimal locations of the surface electrodes on either side of the anterior axillary line. To optimize the skin-to-electrode conduction of the diaphragmatic EMG signal, the skin was carefully prepared with an abrasive paste, alcohol, and an antiperspirant solution (2). EMG signals were amplified, band-pass filtered (band width 10 Hz to 1 kHz; Gould Inc., Valley View, OH), and displayed on a storage oscilloscope (Gould Inc., Ilford, England). Single bilateral phrenic nerve stimulation was performed using two magnetic stimulators (Magstim 200; Jali Medical Inc., Newton, MA) with two sets of double 40-mm coils (D40-1183.00) that generated a magnetic field of 3.2 Tesla at maximal output. The area of stimulation associated with the CDAP of greatest amplitude was located by moving the stimulating probe around the posterior border of the sternomastoid muscle at the level of the cricoid cartilage (3). Thereafter, all stimulations were delivered with maximal output.

Protocol

Twitch stimulation before the weaning trial. Patients were studied with the head of the bed elevated 30 degrees from the horizontal position. Endotracheal suctioning was performed before the start of the study. Controlled ventilation was first initiated by gradually increasing the back-up rate of the ventilator until the patient's inspiratory muscle activity was suppressed (4). Tidal volume (653 ± 3 ml), inspiratory flow (63 ± 3 liters/minute), fractional concentration of inspired oxygen (0.40), and the set level of positive end-expiratory pressure (5 cm H₂O in all instances) were kept constant.

To avoid twitch potentiation (a transient increase in the amplitude of the twitch Pdi when nerve stimulation is preceded by a forceful muscle contraction)(5,6), the patients received controlled ventilation for 20 minutes before delivering the first stimulation. Six to 15 stimulations of the phrenic nerve were delivered bilaterally at intervals of about 15 seconds at end-exhalation while closing the in-line valve (to achieve quasi-isometric conditions and to avoid dissipation of Pes). After the last stimulation, maximal voluntary inspiratory efforts were recorded during a 20-second occlusion of the airway (7).

Trial of spontaneous breathing. The patient was maintained in the same semirecumbent position and breathed through a T-tube circuit receiving the same fractional inspired oxygen concentration as during mechanical ventilation; applied PEEP was zero in all patients. The trial was continued for up to one hour as tolerated. The a priori criteria for termination of the trial were tachypnea, increased accessory muscle activity, diaphoresis, facial sign of distress, cyanosis, tachycardia, arrhythmias, and hypotension (4). Arterial blood samples were collected for blood gas analysis about two minutes into the weaning trial and at the end of the trial in eight weaning failure and four weaning success patients.

Twitch stimulation after the trial. After the weaning trial, both the failure and success patients were returned to mechanical ventilation for about 30 minutes. At the end of this period, twitch Pdi and maximal voluntary inspiratory efforts were measured in all patients (7). In 12 patients, the maximality of phrenic nerve depolarization under relaxed

conditions was assessed by at least one twitch at progressively increasing outputs from the stimulator (from 60% to 100% of possible output). In 6 of the 12 patients, the amplitudes of the right and left CDAPs were within 10% of the maximum values when the output of the stimulator was set at 90% of maximum or less. In 2 patients, the amplitude of the right and left CDAPs were within 10% of the maximum value when the output of the stimulator was set at 95% of maximum. Among these 8 patients (5 weaning failure patients) in whom maximal stimulation was achieved, mean twitch Pdi was 10.8 ± 2.5 cm H₂O. Among the remaining 4 patients (1 weaning failure patient) in whom maximality was not achieved (on the left side in 3 patients and on the right in 1 patient), mean twitch Pdi was 8.6 ± 2.2 cm H₂O ($p = 0.59$). Twitch Pdi was not observed to decrease after the weaning trial in either the 8 patients with evidence of maximal activation or in the 4 patients with submaximal activation. Twitch Pdi not change or decreased by less than 10% in 78% of the weaning failure patients, and none displayed a greater than 15% decrease in twitch Pdi.

Twitch interpolation. In seven patients, extent of diaphragmatic recruitment during the maximal voluntary inspiratory effort was assessed by delivering a single stimulation to the phrenic nerves while the patients performed maximal voluntary inspiratory efforts (i.e., twitch interpolation) (3).

Physiologic measurements

Transdiaphragmatic twitch pressure. Individual twitches were accepted for analysis if they displayed: (1) consistent end-expiratory lung volume before each

stimulation, as reflected by constancy of Pes, (2) absence of esophageal peristalsis at the time of the twitch stimulation, (3) a less than 20% decrease in amplitude of CDAP (either hemidiaphragm) after weaning as compared with that before weaning, (4) absence of electrocardiographic artifact on CDAP, and (5) relaxation of the diaphragm (as signaled by diaphragmatic EMG activity exceeding baseline)(criteria are modified from (5,6)).

All patients tolerated the stimulations and none asked to be withdrawn from the protocol. During phrenic nerve stimulation, end-expiratory lung volume, as determined by the end-exhalation value of Pes, was 10.8 ± 1.4 cm H₂O before the trial and 10.5 ± 1.7 cm H₂O after the trial in the failure group; the respective values were 9.8 ± 1.3 cm H₂O and 9.3 ± 1.1 cm H₂O in the success group. In one failure patient, the end-exhalation value of Pes was 14.4 ± 0.2 cm H₂O before the trial and -1.8 ± 0.1 cm H₂O after the trial. In one success patient, the end-exhalation value of Pes was 6.5 ± 0.4 cm H₂O before the trial and -1.8 ± 1.1 cm H₂O after the trial. In one patient of the failure group, malfunction of the gastric balloon during and after weaning prevented the accurate measurement of twitch Pdi and Pdimax after the trial. Therefore, twitch Pdi values after the weaning trial were available in 16 of 19 patients. The within-occasion coefficient of variation of twitch Pdi before and after weaning was 10% or less in 17 patients and it was within 12 and 14% in the remaining two patients.

Intrinsic positive end-expiratory pressure. Intrinsic positive end-expiratory pressure (PEEPi) was measured during spontaneous breathing as the negative deflection in Pes between the onset of inspiratory effort (end-expiratory Pes) and the onset of

inspiratory flow (8). Relaxation of the abdominal muscles at the onset of inspiration can contribute to the fall in Pes at the onset of inspiratory effort (9). Accordingly, any increase in gastric pressure (Pga) over the course of the preceding exhalation was subtracted from the Pes signal (10,11).

Pressure-time product for the diaphragm. The pressure output of the diaphragm was quantified as pressure-time product (PTPdi). The PTPdi was calculated as the time integral of Pdi from the start to the end of inspiratory effort (12). PTPdi per minute (PTPdi/min) was calculated as the product of PTPdi per breath and respiratory frequency.

Tension-time index of the diaphragm. Tension-time index of the diaphragm (TTdi) (13), an estimate of diaphragmatic inspiratory effort relative to diaphragmatic strength, was calculated as the product of mean inspiratory Pdi (Pdi)/Pdimax and fractional inspiratory time (T_I/T_{TOT}): $TTdi = (Pdi/Pdimax) \times (T_I/T_{TOT})$.

Ratio of swings in gastric pressure to swings in esophageal pressure. The relative contribution of the rib-cage and expiratory muscles to tidal breathing was assessed as the ratio of swings in Pga to swings in Pes ($\Delta Pga/\Delta Pes$). ΔPes was measured from the beginning of effort to its nadir. ΔPga was measured from the beginning of effort (also identified from the Pes tracing) to its maximum excursion.

Data Analysis

Data were recorded at 2,000 Hz and digitized using a 12-bit analog-to-digital converter connected to a computer. Changes in twitch P_{di} and P_{dimax} of patients with a successful and unsuccessful weaning outcome were compared using unpaired t-tests. For the weaning trial, the data were analyzed at five points in time: the first and last minute of the trial, and three periods taken at equal time intervals between the first and last minute. Measurements were obtained from five consecutive breaths at each point. Data at the five time periods within a group were compared by one-way analysis of variance with repeated measures and Newman-Keuls test of multiple comparisons between individual means when appropriate. Data between the groups were compared by two-way analysis of variance with repeated measures across time. Results are reported as mean and standard error. Some of these measurements are also included in a manuscript that is being considered for publication (2).

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