

Critical Illness and Mechanical Ventilation: Effects on the Diaphragm

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Summary

Although life-saving, mechanical ventilation is associated with numerous complications. These include pneumonia, cardiovascular compromise, barotrauma, and ventilator-induced lung injury. Recent data from animal studies suggest that controlled mechanical ventilation can cause dysfunction of the diaphragm, decreasing its force-generating capacity—a condition referred to as ventilator-induced diaphragmatic dysfunction (VIDD). The decrease in diaphragmatic contractility is time-dependent and worsens as mechanical ventilation is prolonged. Evidence supporting the occurrence of comparable diaphragmatic dysfunction in critically ill patients is scarce, although most patients receiving mechanical ventilation display profound diaphragmatic weakness. Atrophy, fibers remodeling, oxidative stress, and structural injury have been implicated as potential mechanisms of VIDD. The decrease in diaphragmatic force that occurs during controlled mechanical ventilation is attenuated during assisted modes of ventilation. Whether the decrease in diaphragmatic contractility observed during controlled ventilation contributes to failure to wean from the ventilator is difficult to ascertain. Weaning-failure patients have reasons other than VIDD for respiratory-muscle weakness. Until we have further data, it seems prudent to avoid the use of controlled mechanical ventilation in patients with acute respiratory failure. *Key words: mechanical ventilation, complications, pneumonia, cardiovascular, barotrauma, ventilator, lung injury, diaphragm, weakness, atrophy, fiber remodeling, oxidative stress, acute respiratory failure.* [Respir Care 2006;51(9):1054–1061. © 2006 Daedalus Enterprises]

Introduction

Mechanical ventilation is life-saving in patients with acute respiratory failure. However, prolonged mechanical ventilation is associated with numerous complications.

Pneumonia, cardiovascular compromise, and barotrauma have been well recognized for decades as potential complications.¹ In the late 1970s, ventilator-induced lung injury (VILI) in injured lungs became recognized as a serious complication of mechanical ventilation.²

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Recently, data have emerged implicating the ventilator as a possible cause of diaphragm dysfunction, decreasing the diaphragm's force-generating capacity—a condition referred to as ventilator-induced diaphragmatic dysfunction (VIDD).³

Parallel With Ventilator-Induced Lung Injury

Much of the motivation for the focus on VIDD comes from experience with VILI. To place VIDD in historical perspective, it is useful to briefly glance back on VILI. From the earliest days of mechanical ventilation, clinicians recognized that mechanical ventilation could damage the lung—causing alveolar rupture and pneumothoraces.¹ In 1974, Webb and Tierney showed that high ventilator pressure could cause ultrastructural injury, independently of air leaks.⁴ Their observation went largely unnoticed until 10 years later, when several investigators confirmed and extended their observations.² Electron-microscopy studies with laboratory animals confirmed that alveolar overdistention causes changes in epithelial and endothelial permeability, alveolar hemorrhage, and hyaline-membrane formation. These studies, however, were greatly criticized and were considered to have minimal relevance to the clinical situation.

Then, in 1990, a report demonstrated that lowering the tidal volume (V_T) caused a 60% decrease in the expected mortality rate among patients with acute respiratory distress syndrome (ARDS).⁵ Subsequently, randomized trials were undertaken.^{6,7} In a study with 861 patients, the ARDS Network investigators reported a 22% difference in mortality between V_T of 6 mL/kg and 12 mL/kg.⁸ It is now generally accepted that the use of high V_T in patients with ARDS is associated with high mortality.^{9,10} Whether the use of low V_T confers a survival advantage is controversial.^{10–12}

Evidence of the Existence of VIDD

The first data that suggested that the ventilator might be causing damage to the respiratory muscles were from animal studies.^{13–15} In rats, 2 days of controlled mechanical ventilation (CMV) reduced the pressure-generating capacity of the diaphragm by 42%, compared with control animals that breathed spontaneously (Fig. 1).¹⁶ The decrease in diaphragmatic force is time-dependent, becoming evident as early as 12 hours in rats,¹⁷ and worsens as mechanical ventilation is prolonged.³

The decrease in diaphragmatic contractility during CMV is not due to changes in lung volume or abdominal compliance.^{13,14} Moreover, nervous-impulse transmission remains intact, since conduction time of the phrenic nerve remains unchanged from day 1 to day 5 of CMV.¹⁴ The decrease, however, in the amplitude of the compound muscle action

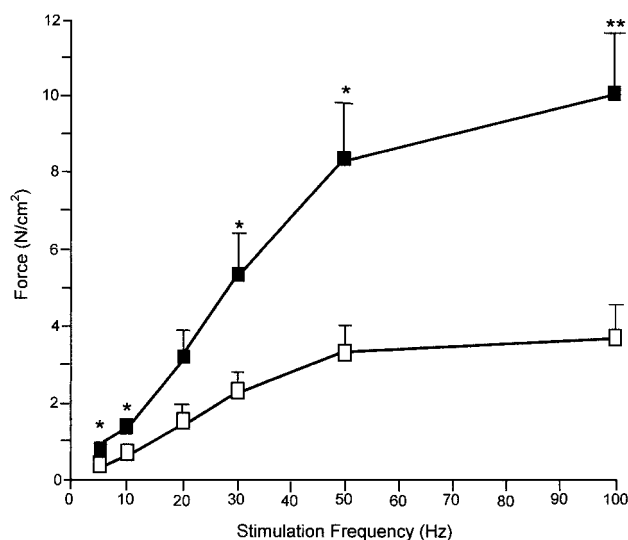


Fig. 1. Diaphragmatic force-versus-frequency curves obtained from mechanically ventilated animals (open boxes) and in control animals (black boxes). Controlled mechanical ventilation generated less force at all frequencies except 20 Hz. (From Reference 16, with permission.)

potential during CMV suggests that the muscle-cell membrane and/or excitation-contraction-coupling apparatus may be involved in the diaphragmatic dysfunction.^{3,14}

Though the evidence supporting the occurrence of VIDD in animal models is strong, comparable data for its occurrence in patients are scarce. Part of the problem is the presence in critically ill patients of confounding factors, such as underlying disease state, different modes of mechanical ventilation, medications, and newly acquired complications, which can also impair diaphragmatic function.¹⁸ Nevertheless, some data exist to support the presence of VIDD in patients.^{19–21} When twitch transdiaphragmatic pressure obtained via magnetic phrenic-nerve stimulation was measured in mechanically ventilated patients, the values were lower than values reported in ambulatory patients with chronic obstructive pulmonary disease (Fig. 2). Such marked reduction of the twitch pressure in most of the patients indicates profound respiratory-muscle weakness.

Mechanism

Muscle Atrophy

In animals, CMV has been shown to contribute to diaphragmatic wasting.^{16,22,23} Muscle atrophy occurs as early as 18 hours after instituting mechanical ventilation.²³ Such atrophy occurs to a greater extent in the diaphragm than in peripheral skeletal muscles, which are also inactive during CMV.^{16,22} In rabbits, 2 days of CMV with positive end-expiratory pressure (PEEP) induced atrophy,²⁴ whereas 3 days of CMV without PEEP was not associated with at-

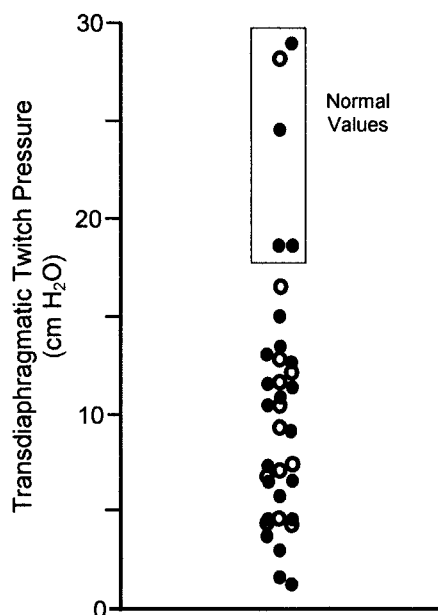


Fig. 2. Transdiaphragmatic twitch pressure in mechanically ventilated patients recovering from acute respiratory failure. The open circles represent data points from Cattapan et al.¹⁹ The black circles represent data points from Watson et al.²⁰ The box represents the range of transdiaphragmatic twitch pressures recorded in ambulatory patients who had severe chronic obstructive pulmonary disease. Most mechanically ventilated patients had evidence of severe diaphragmatic weakness. (From Reference 21, with permission.)

rophy.¹⁵ These findings suggest that PEEP may increase the rapidity of atrophy.

Supporting evidence from humans for the presence of atrophy during CMV is histopathological data from infants.²⁵ In 13 neonates who received mechanical ventilation for 12 days, retrospective analysis of histological data obtained immediately before death showed diffuse atrophy of the diaphragmatic fibers. Such changes were not present in either the diaphragm or extradiaphragmatic muscles of patients ventilated for less than 7 days (Fig. 3).²⁵

Atrophy can result from decreased protein synthesis, increased protein degradation, or both.²⁶ In rats, 6 hours of mechanical ventilation produced a 30% decrease in the rate of mixed muscle protein synthesis and a 65% decrease in the rate of myosin heavy-chain-protein synthesis; this decrement persisted throughout the 18 hours of CMV.²⁷

Increased protein degradation has been observed in animals exposed to 18 hours of CMV.²³ Mammalian cells have 3 systems of proteases for intracellular protein degradation: lysosomal proteases, calpains, and the proteasome system.²⁶ Of these three, the calpains and the proteasome system are considered important for proteolysis during disuse atrophy. Shanely et al.²³ found that the diaphragmatic atrophy that resulted from 18 hours of CMV (in the absence of neuromuscular blocking agent) in rats

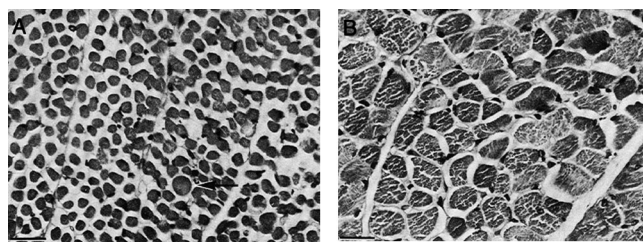


Fig. 3. Diaphragmatic myofibers from an infant ventilated for 47 days (left) and an infant ventilated for 3 days (right) until death. Small myofibers with rounded outlines were seen in the infant who received prolonged mechanical ventilation. (From Reference 25, with permission.)

was caused by increased proteolysis, as indicated by a 46% increase in release of tyrosine. The activities of 2 proteolytic enzymes were increased: calpain-like activity more than doubled (128%), and 20S proteasome activity increased almost 5 times (470%).

Fiber Remodeling

Muscle fibers of the diaphragm (skeletal muscles) are traditionally classified into either slow-twitch (type I) or fast-twitch (type II), based on the heavy-chain composition of the myosin molecule. Modifications of these myosin heavy chains within the diaphragm occur during CMV.^{22,23} After 18 hours of CMV, type I and type II fibers are both decreased in rats, with type II having the greater decrease.²³ In rabbits, 2 days of mechanical ventilation reduced the cross-sectional area of type IIa and type IIb but not type I fibers.²⁴ Because the force generated by type I (slow) fibers is less than that of the type II (fast) fibers, a transformation from fast to slow fibers may contribute to the decrease in force production by the diaphragm during CMV.²⁸ Prolonged duration of CMV (2–4 d), however, results in a different pattern of fiber modification: a decrease in type I fibers and an increase in the number of hybrid fibers, which coexpress both slow and fast myosin heavy-chain isoforms.²² This change from slow to fast fibers may reduce the endurance of the diaphragm, because fewer slow, fatigue-resistant fibers are available.²⁹

Oxidative Stress

An increase in oxidative stress, reflected by an increase in protein oxidation and lipid peroxidation, has been observed in animals within 6 hours of CMV.^{23,30} Oxidative injury is important, because oxidant stress can contribute to both muscle atrophy and contractile dysfunction.³¹ When proteins are oxidized, they become more susceptible to proteolytic attack by the proteasome pathway of protein degradation.³² In addition, oxidative stress can modify sev-

eral proteins associated with excitation-contraction coupling and contribute to a reduction in muscle force production.³³ Protein oxidation during CMV was apparent in insoluble protein with molecular masses of about 200 kD, 128 kD, 85 kD, and 40 kD. These findings raise the possibility that actin (40 kD) and/or myosin (200 kD) undergoes oxidative modification during CMV.³⁰ The specific identification of these modified proteins awaits confirmation.

Antioxidant supplementation attenuates the deleterious effects of CMV on the diaphragm. In rats, the administration of the antioxidant Trolox during CMV attenuated both contractile dysfunction and muscle proteolysis in the diaphragm.³⁴ In critically ill surgical patients, treatment with antioxidant therapy (vitamins E and C) resulted in shorter duration of mechanical ventilation, as compared to patients receiving usual care.³⁵ It is conceivable that some of the beneficial effects of antioxidants were mediated by the prevention of VIDD.

Structural Injury

Structural abnormalities of different subcellular components of diaphragmatic fibers have been observed after 48 hours of CMV.^{15,36} The abnormalities include disrupted myofibrils, abnormal swelling of mitochondria, lipid droplets, and vacuoles.^{15,36} Similar alterations were observed in the external intercostals of ventilated animals, but not in the hind limb muscle. The structural alterations in the myofibrils were inversely related to force output of the diaphragm, accounting for 66% of the reduction of tetanic force ($r = -0.82$) (Fig. 4).¹⁵ The mechanisms for the damage are unclear but may involve activation of ubiquitin-proteasome proteolysis, calpain proteolysis, and oxidative stress.^{3,23}

Clinical Relevance

Mode of Mechanical Ventilation

Most of the evidence for VIDD comes from studies in which CMV was exclusively used. In a study that compared diaphragmatic function during assist-control ventilation versus CMV, Sassoon et al³⁷ found that the contractile response of rabbit diaphragm to tetanic stimulation was decreased by 48% after 3 days of CMV. The decrease in force after assist-control ventilation was much less (14%), though the difference was not statistically significant (Fig. 5). The attenuation of the diaphragmatic-force-loss induced by CMV with the use of assist-control ventilation suggests that VIDD is unlikely to be an important problem in patients who require mechanical ventilation. Very few patients are ventilated with CMV; instead, more than 90% are ventilated with some triggered, assisted mode.³⁸

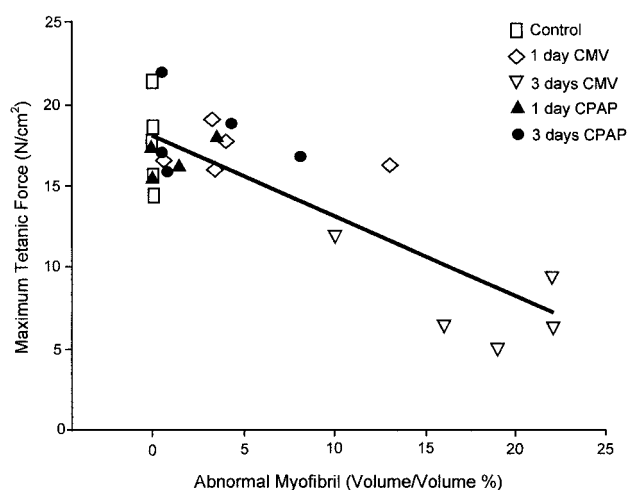


Fig. 4. Relationship between maximum tetanic force and percent of abnormal myofibrils in control, 1 day of continuous positive airway pressure (CPAP), 3 days of CPAP, 1 day of continuous mandatory ventilation (CMV), and 3 days of CMV. The decrease in diaphragmatic force correlated with the volume density of abnormal myofibers ($r = -0.82$, $p < 0.01$). (From Reference 15, with permission.)

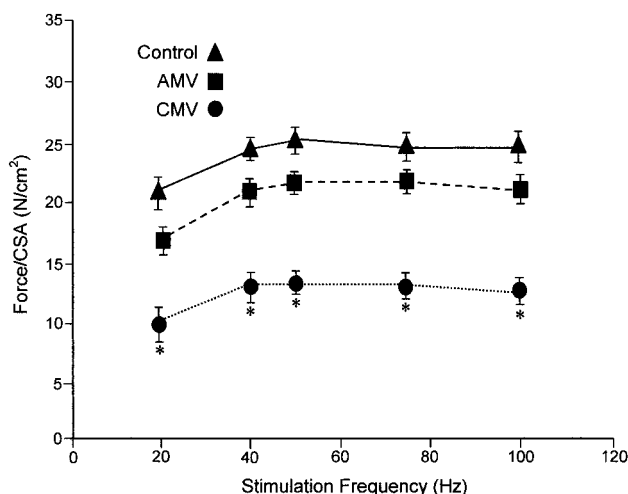


Fig. 5. Diaphragmatic tetanic force (forced divided by cross-sectional area [CSA]) at various stimulation frequencies in control, assist-control mechanical ventilation (AMV), and controlled mechanical ventilation (CMV). * $p < 0.01$ for CMV versus control and AMV. AMV attenuated the force-loss induced by CMV. (From Reference 37, with permission.)

Weaning From Mechanical Ventilation

VIDD may be an important factor in determining why a patient fails to wean from mechanical ventilation. To judge the likelihood that VIDD contributes to weaning failure, it is important to review the data on the mechanisms of weaning failure. The potential mechanisms of weaning failure are abnormal control of breathing, psychological

problems, abnormal mechanics, impaired oxygen delivery to the muscles, and abnormal respiratory muscles.³⁹

Abnormality in the Control of Breathing. Weaning-failure patients commonly develop CO₂ retention,^{40,41} so it is reasonable to expect that the hypercapnia would be accompanied by a decrease in respiratory drive. In 17 patients who failed a T-tube weaning trial, the total pressure generated by the inspiratory muscles, expressed as pressure-time product, increased in all but one patient between the beginning and end of the trial.⁴⁰ Thus, these patients do not typically develop a fall in respiratory motor output. The observation that a decrease in drive is rare in weaning-failure patients, together with the observation that impaired neural function is not a necessary condition for the development of VIDD in animals, can be viewed as indirect evidence of the likelihood that VIDD may contribute to weaning failure, though admittedly the reasoning is somewhat circuitous.^{14,40}

Psychological Problems. In about 20% of weaning-failure patients, the degree of abnormality of respiratory pathophysiology is not different from that seen in weaning-success patients.⁴⁰ It is reasonable to infer that many of these patients fail weaning because of psychological problems. Linking VIDD with the development of these psychological problems is difficult to envision. Nevertheless, VIDD, if it occurs in patients, probably contributes to the duration of ventilator dependence, and that would aggravate psychological problems.

Abnormalities in Lung Mechanics. Patients who fail a weaning trial have higher inspiratory resistance, dynamic elastance, and intrinsic PEEP than patients who successfully wean, and these 3 variables deteriorate over time in the failure patients (Fig. 6).⁴⁰ That is, patients who fail a weaning trial display progressive worsening of their pulmonary mechanics, resulting in large increases in work of breathing. Clearly, the work load imposed by these abnormalities in lung mechanics would be a large challenge for muscles affected by VIDD. But, again, linking VIDD directly as a cause of these lung abnormalities is difficult to imagine.

Impaired Oxygen-Delivery to Muscles. Weaning-failure patients develop cardiovascular dysfunction during a weaning trial.^{42,43} Specifically, weaning-failure patients develop a relative decrease in O₂ delivery (due to an increase in right and left ventricular afterload) associated with an increase in O₂ extraction, leading to a substantial decrease in mixed venous oxygen saturation (Fig. 7).⁴³ Again, it is difficult to determine if these abnormalities in oxygen delivery are the direct result of VIDD.

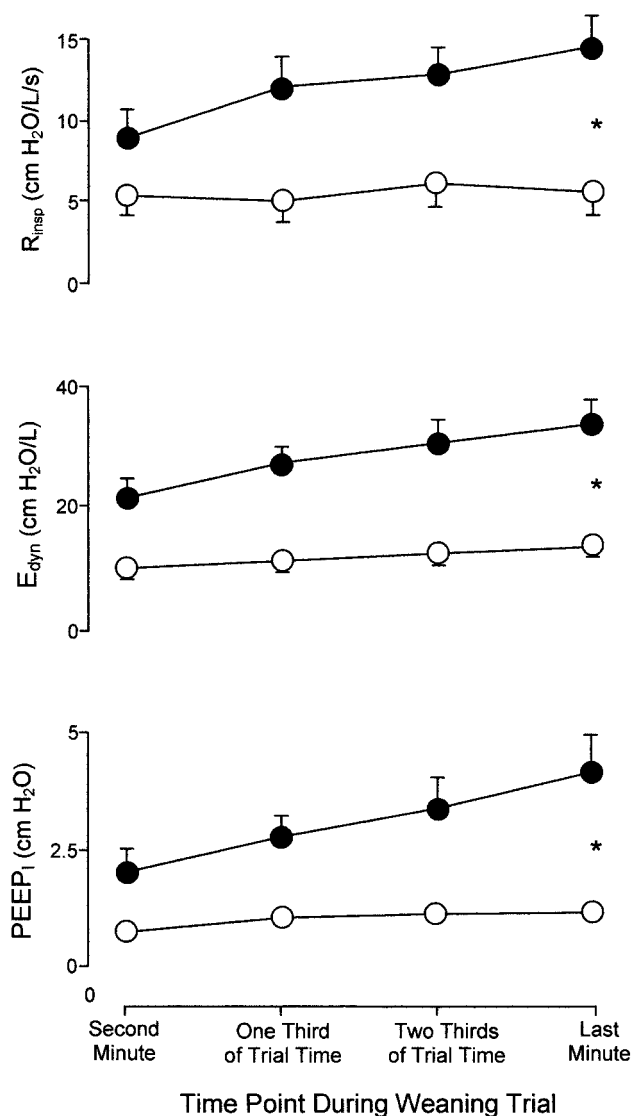


Fig. 6. Inspiratory resistance of the lung (R_{insp}), dynamic elastance of the lung (E_{dyn}), and intrinsic positive end-expiratory pressure ($PEEP_i$) in 17 weaning-failure patients and 14 weaning-success patients. The measurements were obtained at the second minute of the trial, at one third and two thirds of the trial duration, and at the last minute of the trial. Between the onset and end of the trial, the failure group developed increases in R_{insp} ($p < 0.009$), E_{dyn} ($p < 0.0001$), and $PEEP_i$ ($p < 0.0001$), whereas the success group developed increases in E_{dyn} ($p < 0.006$) and $PEEP_i$ ($p < 0.02$). Over the course of the trial, the failure group had higher R_{insp} ($p < 0.003$), E_{dyn} ($p < 0.006$), and $PEEP_i$ ($p < 0.009$) than the success group. (From Reference 40, with permission.)

Abnormalities of the Respiratory Muscles. When considering respiratory-muscle pathophysiology, it is useful to make a distinction between respiratory-muscle strength and endurance (the inverse of fatigue). One way of demonstrating fatigue is to externally stimulate the phrenic nerve and measure the contractile response of the diaphragm.^{44,45} Laghi et al⁴⁴ measured twitch transdiaphragmatic pressure,

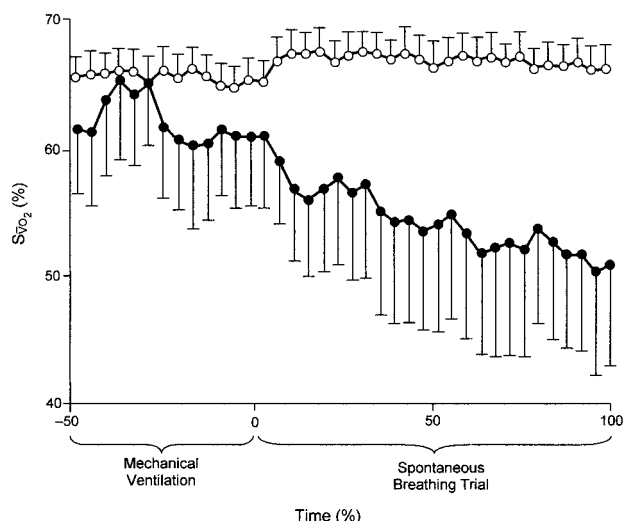


Fig. 7. Ensemble averages of interpolated values of mixed venous oxygen saturation (S_{vO_2}) during mechanical ventilation and during a spontaneous breathing trial, in patients who succeeded in the trial (open circles) and patients who failed the trial (black circles). During mechanical ventilation, S_{vO_2} was similar in the 2 groups. Between the beginning and end of the trial, S_{vO_2} decreased in the failure group ($p < 0.01$), whereas it remained unchanged in the success group. Over the course of the trial, S_{vO_2} was lower in the failure group than in the success group ($p < 0.02$). (From Reference 43, with permission.)

using phrenic stimulation, in 11 weaning-failure patients and 8 weaning-success patients before and after a T-tube weaning trial (Fig. 8). No patient in either group exhibited a fall in twitch pressure, which would indicate the presence of fatigue. Most likely the patients did not develop fatigue because physicians reinstated mechanical ventilation before there was enough time for fatigue to develop. The relationship between tension-time index and the length of time that a load can be sustained until task-failure follows an inverse power function. Bellemare and Grassino⁴⁶ expressed the relationship as:

$$\text{Time to task-failure} = 0.1 (\text{tension-time index})^{-3.6}$$

Using the latter equation and repeated measurements of tension-time index, it is possible to estimate how much longer the patient should be able to sustain that load during a weaning trial. Accordingly, at the end of the trial (ie, the point that the physician reinstated mechanical ventilation), the patients were predicted to be able to sustain an additional 13 min of spontaneous breathing before developing task-failure. In other words, clinical manifestations of severe respiratory distress were evident for a substantial period before the patients were predicted to develop fatigue. In an intensive-care setting these clinical signs will lead clinicians to reinstitute mechanical ventilation before fatigue has time to develop.³⁹

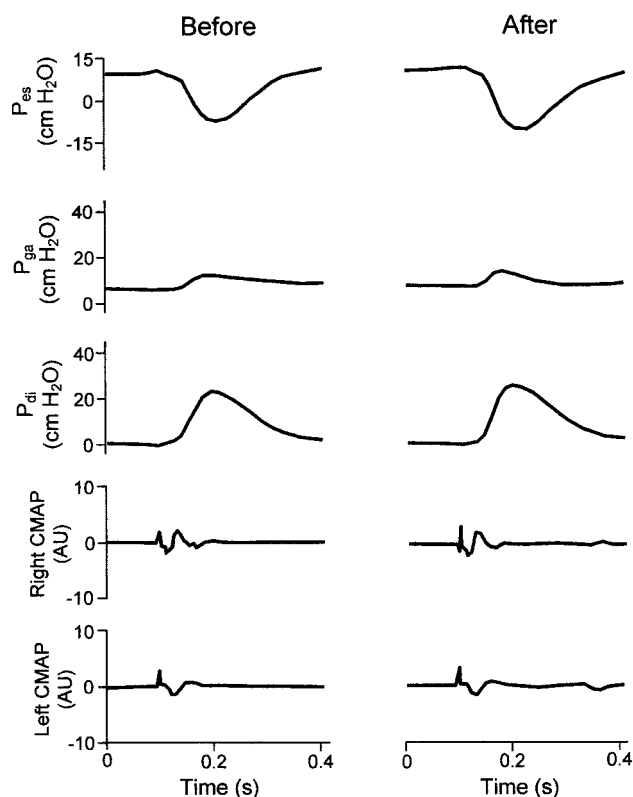


Fig. 8. Esophageal pressure (P_{es}), gastric pressure (P_{ga}), transdiaphragmatic pressure (P_{di}), and compound motor action potentials (CMAP) of the right and left hemidiaphragms, after phrenic-nerve stimulation before (left) and after (right) a T-tube spontaneous breathing trial in a weaning-failure patient. The end-expiratory P_{es} and the amplitude of the right and left CMAPs 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 P_{di} elicited by phrenic-nerve stimulation was the same before and after weaning. AU = arbitrary units. (From Reference 44, with permission.)

The overall strength of the inspiratory muscles is usually assessed by measuring the transdiaphragmatic pressure generated during a maximal inspiratory effort against an occluded airway. In patients undergoing a weaning trial, the maximal inspiratory transdiaphragmatic pressure did not differ between success and failure patients, and the values did not decrease after the trial in each group.⁴⁴ While maximal inspiratory transdiaphragmatic pressure did not differ between the successes and failures, the values were considerably lower than the values from stable outpatients with severe chronic obstructive pulmonary disease.⁴⁷ These data indicate that weaning-failure patients have severe respiratory-muscle weakness.

The respiratory muscles can be weak in a critically ill patient for reasons other than VIDD (Table 1). Causes of weakness include neuromuscular blockers, critical illness polyneuropathy, hyperinflation, shock, ongoing sepsis, ma-

Table 1. Causes of Decreased Strength in Weaning-Failure Patients

Neuromuscular blockers
Neuromuscular disorders (critical-illness polyneuropathy)
Hyperinflation
Shock and ongoing sepsis
Malnutrition and electrolyte disturbances
Ventilator-induced diaphragmatic dysfunction

for malnutrition, and electrolyte disturbances.⁴⁴ Of these, the confounding effects of neuromuscular blockers, critical illness polyneuropathy, and hyperinflation can be excluded. Animal studies have demonstrated the development of VIDD in the absence of neuromuscular blockers^{15–17} and shown that VIDD occurs despite intact neuromuscular transmission, which indicates that critical illness polyneuropathy is an independent condition from VIDD.¹⁴ Instead of the nerves being involved, VIDD appears to arise primarily within the myofibers.^{3,14} The decrease in force-generating capacity in VIDD is not caused by hyperinflation, because transpulmonary pressure and dynamic lung compliance are not altered.¹⁴ The animals that developed VIDD were not in shock, septic, malnourished, or suffering from electrolyte abnormalities.³ Of course, all of these factors may modulate the development of VIDD in animals. The frequent occurrence of these problems in weaning-failure patients makes it very difficult to infer that muscle weakness caused by VIDD is the main cause of weaning failure in a given patient. Clearly, it would help to have a sensitive and specific diagnostic test for VIDD for use with patients, such as ultrasound, that would detect diaphragmatic atrophy, a biopsy that would reveal pathognomic evidence of damage (in an accessible muscle, such as an intercostal), or a blood test that indicated diaphragmatic damage. At present, such tests do not seem to be attainable. If such a test were available, the role of VIDD in patients would be easier to solve.

To develop a test, a clear definition of VIDD is needed. An operational definition might be “respiratory-muscle weakness in a ventilated patient without any other explanation for the weakness.”²⁹ But that definition is too general and imprecise to be of much help. In any ventilated patient there are usually numerous other potential explanations for respiratory-muscle weakness. At a pathological level, a definition for VIDD needs to take into account both muscle atrophy and muscle injury.

However, the absence of a diagnostic test for VIDD should not block progress on clinical research on this subject. To date there is no diagnostic test for VILI. The best one can say is that a patient with plateau pressure above about 32 cm H₂O is at risk for VILI.⁹ Incontrovertible evidence of VILI has not been shown in even one patient, although VILI is very frequently suspected.² Inferring the presence of VILI, however, is not the same as being able

to diagnose it with certainty in a given patient. Nevertheless, the conceptual framework for VILI has led to the identification of ventilator settings that are harmful to patients with ARDS. The challenge is to identify new approaches to mechanical ventilation that will decrease the likelihood of VIDD.

Summary

Substantial evidence from animal models indicates that CMV can damage previously normal muscles, but there are very little data to indicate that VIDD occurs in critically ill patients or whether it may be a contributing factor to weaning failure. The knowledge acquired about VILI has altered ventilator management in patients with ARDS, resulting in improved outcomes. The challenge is to take lessons gained from research on VIDD and use it to lead to changes in how better to set the ventilator to avoid VIDD.

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Discussion

Panitch: Regarding the data from Laghi et al^{1,2} on sequential tension-time indices, was the maximum P_{di} [transdiaphragmatic pressure during a maximum inspiratory effort] measured every 10 minutes? And if there's no change in P_{di} , and presumably no change in maximum P_{di} , do we have to presume it's all because the inspiratory time increases—the ventilatory pattern changes?

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Jubran: The answer to the first question is no. Maximum P_{di} was measured before the trial and after the end of the trial. We did not measure maximum P_{di} during the trial. I suspect that maximum P_{di} goes down. I don't believe it's a timing problem, because in our previous studies on weaning we found that T_I/T_{tot} [ratio of inspiratory time to total-respiratory-cycle time] and respiratory rate did not change during the trial, so I believe it's a problem of maximum P_{di} .

Panitch: We've tried to use the tension-time index in children who have been ventilated for prolonged periods. We see if we can extend the spontaneous breathing trials longer and longer. We advance the trial duration a certain amount, and then put the patient back on ventilation; we've tried to use this to help guide us. Do you think there is a difference in the predictability of the test in patients who are ventilated for, say, a couple of weeks versus a month or more?

Jubran: The only data I have are for f/V_T [respiratory frequency divided by

tidal volume, which is the rapid-shallow-breathing index]. In the original study, Yang and Tobin¹ found f/V_T to be very accurate in predicting weaning outcome in patients who received short-term mechanical ventilation, which they defined as less than 7 days. The predictive power of f/V_T , however, was worse after 7 days. So I think there is a difference between the duration of mechanical ventilation and whether you can use these predictive indices.

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Deem: Amal, assuming that VIDD does exist, how can we distinguish it from other causes of diaphragmatic dysfunction, including critical-illness myopathy?

Jubran: I don't see how we can distinguish VIDD from other causes of diaphragmatic dysfunction. VIDD is diagnosed by exclusion. If you're confident that all the factors that I went through today do not exist, then you can say, "By exclusion, this patient may have VIDD." But, again, VIDD has been demonstrated in animals during CMV, so if the patient has been on CMV for 4 days, has not received steroids or neuromuscular blockers, and does not have any other identifiable cause of respiratory-muscle weakness, then you can perhaps infer that he has VIDD.

Benditt: I was struck by the fact that it looked like the respiratory load was increasing with the weaning trial. What is it that's starting that sort of cascade and causing worse compliance?

Jubran: The one thing we know that occurs right away is rapid shallow breathing. Let me go back to the load issue. We measured the load during

mechanical ventilation, right before we placed the patient on a T-piece. We found no difference between the successes and the failures, so the lung mechanics were the same. When we placed them on a T-piece, they instantly separated themselves out. So I believe the breathing pattern may be contributing to the worsening of the mechanics. For example, I know auto-PEEP [intrinsic positive end-expiratory pressure] is going up, probably because the rate is going up. The elastance is going up, probably because of the frequency-dependence of compliance. But why does the resistance go up? I can't explain it.

Lechtzin: Whether or not VIDD exists or is a problem, the antioxidant data you showed are very interesting, and there doesn't seem to be any downside to giving antioxidants. Do you give antioxidants clinically?

Jubran: No, because I am not convinced yet that VIDD is clinically important. We need more data.

Deem: That study was performed at Harborview Hospital in Seattle, and the study was with surgical patients.¹

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Benditt: Are they still doing that?

Deem: The trauma surgeons do use it, yes. The medical and neurosurgical ICUs do not use vitamin supplementation.

Pierson*: My question is about how big a list really exists of the potential

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causes of weaning failure. Failure of ventilatory drive is easy to identify: patients don't breathe when you give them the opportunity. The occasional patient will have oxygenation problems; that's not very common, but it's also easy to identify. I submit that all other cases of weaning failure are because of the discrepancy between the patient's ventilatory demand and ventilatory capabilities. So my question for you is this: aside from the variability in different patients with respect to how they react to that discrepancy, what evidence is there that there is any such thing as a psychological reason for weaning failure?

Jubran: When we looked at the reasons why 17 patients failed weaning, based on the measurements we had, we found that fourteen had a problem with load versus capacity, which we quantified as esophageal pressure over maximum airway pressure. Three of the patients, however, did not show any problems with load versus capacity. Physiologically, they behaved just like weaning-success patients, yet they failed the weaning trial. They had no problems with gas exchange or mechanics, so we speculated that these 3 patients failed because of psychological problems.

Pierson: So in what respect, did they fail? Or was it the doctor who failed?

Jubran: Was it the doctor who failed? Obviously, I can't answer that one, but it was the physician at the bedside—it wasn't me—who was making that decision. The patient just didn't look good to him, so he put him back on the ventilator.

Pierson: Having been interested in weaning for a long time, and also being a bedside pragmatist, I've observed that house staff very often invoke the concept of psychological unweanability. I've been trying to pay attention to this when it comes up, and in every case I've been aware of in recent years,

it's been no problem for me to demonstrate that there is a discrepancy between this patient's mechanical abilities and the load that's placed on them. So I've become increasingly skeptical about purely supratentorial reasons for not being able to be weaned from the ventilator. And my suspicion is that the caregiver's subjective impression of respiratory distress in the patient is what results in the patient either not being given the opportunity to wean or a spontaneous breathing trial being curtailed.

Jubran: Anxiety and depression are very tough areas to study. I share your views about the importance of anxiety in the ICU. Quite often the house staff says the same things to me: "The patient's too anxious, and we're not going to wean him." You measure the blood gases and find that P_{aCO_2} is 70 mm Hg, so you can understand why he is anxious. However, I have changed my views on the importance of anxiety during weaning, based on data we have in patients at our long-term weaning center. The patients typically have been on the ventilator for 30 days prior to arrival at the weaning facility. As soon as they arrive at the facility, they are evaluated by a psychologist. Their initial evaluations indicate that about 60% of the patients are anxious. Now, is the anxiety causing the patient to be dependent on the ventilator? Obviously, we can't say that, but I suspect that anxiety is more prevalent than we think it is. The problem is that, like VIDD, we don't know how to diagnose it.

Benditt: Has anybody tried with animal studies to compare negative-pressure ventilation with positive-pressure ventilation?

Jubran: No. Only positive-pressure ventilation has been studied, mostly using CMV. Sassoon did study animals during assist-control ventilation.¹

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Hess: How might dyspnea play into this? Are the patients complaining of increasing dyspnea, and the bedside clinician is responding to that and putting the patient back on the ventilator?

Jubran: Dyspnea is a fascinating topic, but very few studies have measured dyspnea in patients who are on the ventilator. Dyspnea is probably one of the most difficult measurements to do. The problem is that the patient must be neurologically intact to get reliable measurements. I am aware of 2 studies in which dyspnea was measured. One study found that dyspnea did not change as the level of SIMV [synchronized intermittent mandatory ventilation] or pressure support was decreased.¹ The other study, by Leung, from our group, found that as you decrease the level of pressure support, dyspnea increases.² So the issue of dyspnea in ventilated patients is confusing. Knebel et al¹ also measured anxiety, and they found that changes in dyspnea were related to changes in anxiety, so I suspect that dyspnea and anxiety are interrelated.

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Mehta: Do you think that tachypnea is often used as a sign of failure of a spontaneous breathing trial? We know that respiratory rate varies with gender, age, obesity, and anxiety, and it's one of the few objective variables we have when we're assessing patients.

And often we stop a spontaneous trial because a patient's respiratory rate is above our cutoff of, say, 35 breaths/min, but I think it's a false predictor of unsuccessful extubation.

Jubran: Respiratory rate is probably one of the most misunderstood variables. We have measured respiratory rate on a continuous breath-by-breath basis during a T-piece trial in over 100 different patients and at different centers, and we found that in weaning failure the respiratory rate increases within the first minute of a T-piece trial but then it remains constant throughout the weaning trial. Yang and Tobin were the first to show that f/V_T accurately predicts weaning outcome, and the reason f/V_T performed well is because of tidal volume, not because of rate. So I believe it's a misconception that the rate goes up during a failed trial. When you actually do the measurements, you will find that the rate does not change after the first minute.

Mehta: So are you saying that you use Δf [change in respiratory rate] instead of absolute f ? Would you proceed with the weaning trial even if the frequency is already high?

Jubran: I use the absolute f . I calculate f/V_T , and if f/V_T is over 100 breaths/min/L, I do not proceed with a T-piece trial. If the f/V_T is less than 100 breaths/min/L, then I proceed with a trial.

Hess: If I can follow up on Geeta's point, I think that respiratory rate is often an artificial barrier to discontinuing mechanical ventilation. I'm impressed with how many patients are called "failure to wean" because every time they are taken off the ventilator the respiratory rate goes over 30 breaths/min and they are put back on the ventilator.

Jubran: I agree. Many factors can affect respiratory rate. For example, patients with pulmonary fibrosis typ-

ically have a high respiratory rate during rest.

Upinder Dhand: Amal, I want to understand what you said about the testing of fatigue on the diaphragm twitch. It seemed that only one twitch was used to estimate the pressure, and to compare the success to the nonsuccess. Usually, for muscle fatigue, one twitch is not enough; you have to exercise and then check the twitch. It will be hard to do for the diaphragm, but I think one of the ways would be to give a tetanic stimulation, like a repetitive stimulation over a brief period of time, and then do the twitch.

Jubran: I only showed the data for one twitch, but typically, Franco Laghi does 10 to 15 twitches. He has very strict criteria for accepting what is and is not a good twitch. From those 10 or 15 twitches he may end up with 5. So what I showed is based on several twitches averaged together.