Clinicians have long been aware that substantial lung injury results when mechanical ventilation imposes too much stress on the pulmonary parenchyma. Evidence is accruing that substantial injury may also result when the ventilator imposes too little stress on the respiratory muscles. Through adjustment of ventilator settings and administration of pharmacotherapy, the respiratory muscles may be rendered almost (or completely) inactive. Research in animals has shown that diaphragmatic inactivity produces severe injury and atrophy of muscle fibers. Human data have recently revealed that 18 to 69 hours of complete diaphragmatic inactivity associated with mechanical ventilation decreased the cross-sectional areas of diaphragmatic fibers by half or more. The atrophic injury seems to result from increased oxidative stress leading to activation of protein-degradation pathways. Scientific understanding of ventilator-induced respiratory muscle injury has not reached the stage where meaningful controlled trials can be done, and thus, it is not possible to give concrete recommendations for patient management. In the meantime, clinicians are advised to select ventilator settings that avoid both excessive patient effort and excessive respiratory muscle rest. The contour of the airway pressure waveform on a ventilator screen provides the most practical indication of patient effort, and clinicians are advised to pay close attention to the waveform as they titrate ventilator settings. Research on ventilator-induced respiratory muscle injury is in its infancy and portends to be an exciting area to follow.

The most common reason to institute mechanical ventilation is to decrease patient distress resulting from an increase in work of breathing (1). In this situation, the ventilator functions as an additional set of muscles and decreases the load placed on the patient’s own respiratory muscles. The second major indication for mechanical ventilation is to improve oxygenation in, for example, patients with the acute respiratory distress syndrome (1). A ventilator improves oxygenation by increasing tidal volume and end-expiratory lung volume and by better matching of ventilation and perfusion within the lung parenchyma (2). Although the oxygen-enhancing action of the ventilator is not directed at the respiratory muscles per se, patients with impaired oxygenation commonly receive treatment with antibiotics (3), corticosteroids (4), sedatives (5), and neuromuscular agents (6), all of which can weaken respiratory muscles.

Every patient who survives an episode of acute respiratory failure faces a major challenge at the point of ventilator discontinuation. The main reason that weaning attempts fail in patients is because their work of breathing is high consequent to abnormal lung mechanics (increased resistance and decreased compliance) and their respiratory muscles are unable to cope with the increased load (7). From this account, the performance of the respiratory muscles is a dominant consideration at the point when mechanical ventilation is first instituted and when it is withdrawn.

A major concern of critical care physicians is the growing awareness that mechanical ventilation can harm the lung. From the earliest days of intensive care, it has been recognized that use of high airway pressure can rupture the lung parenchyma, causing pneumothorax. In 1974, Webb and Tierney (8) demonstrated that mechanical ventilation can cause hemorrhagic and edematous lesions independent of barotrauma. This seminal observation was extended by other animal experiments, and the alveolar injury has been shown to result from the use of high tidal volumes; the injury has been named volutrauma or ventilator-induced lung injury (9). Studies in patients followed studies in animals, which culminated in randomized, controlled trials that have shown that use of high tidal volume leads to increased risk for death in patients with the acute respiratory distress syndrome.

Just as mechanical ventilation can damage the lung parenchyma, investigators have postulated that the ventilator can damage the respiratory muscles (10). The fear is
that mechanical ventilation lowers demands on a patient’s respiratory muscles to such an extent that they become inactive, resulting in injury and atrophy at a structural level. In contrast to research on ventilator-induced lung injury, scientific understanding of ventilator-induced respiratory muscle injury has not reached the stage in which meaningful randomized, controlled trials can be done, and thus, it is not possible to give concrete recommendations for patient management. Nevertheless, the accruing biological and pathophysiologic research on the effect of mechanical ventilation on the respiratory muscles is leading many experts to change their approach to ventilator management.

**ANIMAL MODELS OF VENTILATOR-INDUCED MUSCLE INJURY**

During the past 2 decades, several groups have studied the effect of mechanical ventilation on the muscles of laboratory animals. A seminal study showed that 11 days of controlled mechanical ventilation produced a 46% decrease in respiratory muscle strength (11). In that study, animals received neuromuscular-blocking agents to ensure that they made no respiratory efforts. Controlled mechanical ventilation differs from the more commonly used method, assist-control ventilation, in which patients continue to make some respiratory efforts in addition to receiving assistance from the ventilator (12). Subsequent studies have revealed that complete cessation of diaphragmatic activity with controlled mechanical ventilation—alone (13) or in combination with neuromuscular-blocking agents (14)—results in injury and atrophy of diaphragmatic fibers. Muscle fibers generate less force in response to stimulation, not simply because of their decreased bulk but even when they are normalized for cross-sectional area. The decrease in diaphragmatic force ranges from 20% to more than 50%. The alterations in muscle function occur rapidly, within 12 hours of instituting mechanical ventilation (15), and they seem to increase as ventilator duration is prolonged (16).

Increasing experimental evidence suggests that oxidative stress is the most proximal mechanism in the biochemical cascade that leads to ventilator-induced muscle injury (17, 18). Oxidative stress decreases contractility by causing protein oxidation and by promoting protein catabolism (18). Other mechanisms that contribute to muscle protein loss are apoptosis (15) and decreased protein synthesis (19).

The degree of injury in animal studies depends on how the ventilator is set. Sassoon and colleagues (20) have shown that maintenance of some respiratory muscle activity, through the use of assist-control ventilation, seemed to prevent the impairment in diaphragmatic contractility, whereas completely controlled ventilation induced a 48% decrease in contractility. Intermittent bursts of unassisted breathing during a course of controlled ventilation have also been shown to limit injury (21).

In animal models, limb immobilization (with a cast) in a shortened position accelerates protein degradation and causes myonuclear apoptosis (22). Whether the application of positive end-expiratory pressure (and thus shortening of the diaphragm) during controlled mechanical ventilation further aggravates the structural injury caused by muscle disuse remains to be determined.

**EVIDENCE FOR VENTILATOR-INDUCED MUSCLE INJURY IN HUMAN PATIENTS**

Levine and coworkers (23) have recently presented human data that support the findings of the animal studies. They performed biopsies of the costal diaphragms from 14 organ donors who were brain-dead. These patients exhibited diaphragmatic inactivity and had received mechanical ventilation for 18 to 69 hours. They also performed intraoperative biopsies of the diaphragms of 8 patients undergoing thoracic surgery for suspected lung cancer. These control patients had diaphragmatic inactivity and mechanical ventilation for 2 to 3 hours.

Histologic measurements revealed marked diaphragmatic atrophy in the brain-dead patients. The mean cross-sectional areas of muscle fibers were significantly decreased by more than 50% compared with those in the control group. The cross-sectional area of fibers of the pectoralis major, a muscle not affected by mechanical ventilation, was equivalent in the 2 groups. This finding indicates that the diaphragmatic atrophy experienced by the brain-dead patients was not part of some generalized muscle-wasting disorder.

Biochemical and gene-expression studies suggest that the atrophy resulted from oxidative stress leading to muscle protein degradation. A 23% lower concentration of glutathione in the diaphragms of brain-dead patients than in the control patients indicates evidence of oxidative stress (23). A 154% greater expression of active caspase 3 in the brain-dead patients than in the control patients indicates evidence of enhanced muscle protein degradation (23). Caspase is an enzyme that can dissociate proteins from the myofibrillar lattice, a critical step in muscle proteolysis.

Muscle proteolysis typically involves the ubiquitin–proteasome pathway, a cytosolic adenosine triphosphate–dependent protease system (24). In this system, proteins catabolized by the proteasome are first “tagged” with a small chain of ubiquitin molecules. Tagging with ubiquitin is a process that requires adenosine triphosphate and involves specific “ubiquitin ligases,” such as atrogin-1 and muscle-specific ring finger-1 (24). Levine and coworkers (23) found that the number of messenger RNA transcripts for atrogin-1 and muscle-specific ring finger-1 were 200% and 590% greater, respectively, in the brain-dead patients than in the control patients.

On the basis of these findings, Levine and coworkers (23) concluded that 18 to 69 hours of complete diaphragmatic inactivity and mechanical ventilation produced
marked diaphragmatic atrophy as a result of increased oxidative stress leading to activation of protein degradation pathways.

Other human data support the likelihood that mechanical ventilation can induce respiratory muscle atrophy. One group (25) did autopsies in 13 infants who died after receiving mechanical ventilation for more than 12 days and 26 infants who died after receiving ventilation for less than 7 days. The cross-sectional areas of diaphragmatic fibers were much smaller in the infants who received the longer duration of mechanical ventilation. Fibers taken from strap and tongue muscles were similar in the 2 groups. Another group (26) reported a patient with a high spinal cord injury whose diaphragmatic pacemaker did not function on the left side. Ultrasonography done after 8 months of mechanical ventilation revealed atrophy of the left hemidiaphragm. Pacemaker stimulation of the right phrenic nerve for 30 min/d was sufficient to prevent atrophy of the right hemidiaphragm.

Over the past 2 decades, research on respiratory muscle function in ventilated patients has focused mostly on patients at the time of weaning. The pressure generated by a patient during a maximal inspiratory pressure (PImax) maneuver is taken as a measure of respiratory muscle strength. Many studies have shown that PImax values do not discriminate between patients who are and those who are not successfully weaned. These findings led to the belief that respiratory muscle weakness was not a determinant of clinical outcome in ventilated patients. Recent studies have revealed that PImax can misrepresent respiratory muscle strength because the values are heavily influenced by patient motivation and cooperation (24). A more objective measure of diaphragmatic strength is obtained by stimulation of the phrenic nerves and recording the resulting “twitch” transdiaphragmatic pressure (Figure 1). In healthy persons, twitch transdiaphragmatic pressure is 35 cm H₂O (SD, 8 cm H₂O) (27). Ambulatory patients with respiratory muscle weakness secondary to chronic obstructive pulmonary disease have twitch transdiaphragmatic pressures of 20 cm H₂O (SD, 7 cm H₂O) (28). Patients who require mechanical ventilation have much lower twitch pressures, many less than 15 cm H₂O (29, 30). These observations indicate that diaphragmatic weakness in ventilated patients is much greater than previously suspected and suggest that the diaphragmatic atrophy described by Levine and coworkers (23) may be not uncommon. Measurement of twitch pressure has not been evaluated in terms of its reliability as a predictor of weaning.
outcome, and given the considerable skill required to make the measurement it is doubtful that it will ever become a part of everyday clinical practice.

Physicians should not assume that respiratory muscle weakness in a ventilated patient is diagnostic of ventilator-induced muscle injury. Although ventilator injury is one possibility, several other common conditions, including sepsis (24), and the administration of antibiotics (3), corticosteroids (4), sedatives (5), and neuromuscular agents (6), can also induce respiratory muscle weakness (Table).

**IMPLICATION FOR SETTING THE VENTILATOR**

Research on ventilator-induced muscle injury is about 20 years behind research on ventilator-induced lung injury (9, 10). The evidence to date, nevertheless, carries several implications for clinical management. The use of controlled mechanical ventilation and neuromuscular-blocking agents are generally avoided unless a patient continues to fight the ventilator despite all attempts to identify and reverse the cause (2). Animal data suggest that use of assisted-ventilator methods, in which a patient makes some respiratory effort during every ventilator breath, may attenuate the development of diaphragmatic injury (20). Data on this point, however, are very limited. Large reductions in patient effort, short of complete inactivity, may be sufficient to induce muscle injury—although less than that is caused by controlled ventilation. The amount of work that a patient does while a ventilator delivers a breath depends largely on a patient’s respiratory center drive at the point of triggering the ventilator ($r = 0.78$) (Figure 2) (31). Sedative and analgesic agents are widely used in ventilated patients and markedly decrease respiratory drive; these agents may contribute to ventilator-induced muscle injury by decreasing patient work during assisted breaths.

Pressure-time product is the amount of pressure generated by the respiratory muscles during inspiration, and it is commonly used to quantify respiratory effort in research studies. The average value in a healthy person is about 90 cm H$_2$O • s/min (7). For patients in the throes of acute respiratory failure (before receiving mechanical ventilation), the average pressure-time product is about 400 cm H$_2$O • s/min (7). Although pressure-time product is not part of routine clinical practice, it provides a mental framework when selecting ventilator settings. At the time a patient is commenced on mechanical ventilation, ventilator settings are generally adjusted and sedation is titrated to substantially decrease patient effort (aiming for a pressure-time product of about 70 to 110 cm H$_2$O • s/min). We worry that too great a reduction in patient effort (such as a pressure-time product <40 cm H$_2$O • s/min) might result in the development of ventilator-induced muscle injury. We emphasize that our caution is based on circumstantial evidence and that the appropriate tradeoff between increased patient effort and excessive respiratory muscle rest is unknown. Definitive data on patient outcomes are not expected for many years.

**Table. Causes of Respiratory Muscle Weakness**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Example or Mechanism</th>
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<tbody>
<tr>
<td>Preexisting</td>
<td></td>
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<tr>
<td>Neurmuscular disorders</td>
<td>The Guillain–Barré syndrome</td>
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<tr>
<td>Hyperinflation</td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>Malnutrition</td>
<td>Crohn disease</td>
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<tr>
<td>Endocrine disturbances</td>
<td>Hypothyroidism or hyperthyroidism</td>
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<tr>
<td>New onset</td>
<td></td>
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<tr>
<td>Ventilator-associated respiratory muscle injury</td>
<td>Oxidative stress, protein catabolism</td>
</tr>
<tr>
<td>Sepsis-associated myopathy</td>
<td>Oxidative stress, protein catabolism</td>
</tr>
<tr>
<td>Paresis acquired in the intensive care unit</td>
<td>Multiple-organ failure</td>
</tr>
<tr>
<td>Acidosis</td>
<td>Decreased contractility</td>
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<tr>
<td>Electrolyte disturbances</td>
<td>Hypokalemia</td>
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<tr>
<td>Medications</td>
<td>Corticosteroids, aminoglycosides, and neuromuscular-blocking agents</td>
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</table>

Figure 2. Relationship between respiratory drive and patient effort during the time that the ventilator is delivering a breath (measured as inspiratory pressure-time product per breath in cm H$_2$O • s) is closely related to a patient’s respiratory drive (measured as $dP/dt$ in cm H$_2$O/s) at the moment that a patient triggers the ventilator ($r = 0.78$). The inspiratory muscles of a patient who has a low respiratory drive at the time of triggering the ventilator will do very little work during the remainder of inspiration when the ventilator provides assistance. Conversely, the inspiratory muscles of a patient who has a high respiratory drive will expend considerable effort throughout the inspiration, even though the mechanical ventilator is providing assistance. Data are from reference 31.
Airway-pressure waveforms recorded in a patient shortly after the initiation of mechanical ventilation, in a patient making no respiratory effort (controlled mechanical ventilation), and in a patient receiving an appropriate level of assist-control mechanical ventilation. The dotted lines on the left and right waveforms reproduce the tracing achieved by passive, controlled mechanical ventilation as it occurs in a patient receiving neuromuscular-blocking agents. Left. Waveform depicting a patient in respiratory distress who has an excessive work of breathing; this can be inferred from the initial concavity, which results from vigorous inspiratory effort and the spike at the end of ventilator assistance, which is the result of expiratory muscle recruitment. Middle. Waveform depicting a patient making no respiratory effort and, thus, is at risk for ventilator-induced respiratory muscle weakness. Right. Waveform depicting a patient performing an appropriate amount of respiratory work. The small downward dip at the start of the breath indicates the small inspiratory effort required to trigger the ventilator, and the distance between the solid line (actual airway pressure) and the dotted line (expected tracing during controlled ventilation, as in the middle waveform) is proportional to the amount of work done by the patient’s inspiratory muscles while the ventilator is providing assistance. The patient in the right waveform is doing much more respiratory work than the patient in the middle waveform and much less work than the patient in the left waveform.

In everyday practice, the best indicator of patient effort during mechanical ventilation is the contour of the airway pressure waveform on the ventilator screen (32–34). Figure 3 shows 3 waveforms: the typical waveform in a patient soon after institution of mechanical ventilation while the patient still has severe respiratory distress; the waveform produced by controlled mechanical ventilation, in which the patient makes no respiratory effort; and the waveform in which a patient receives an appropriate level of ventilator assistance. Ventilator settings need to be adjusted to navigate a course between the excessive patient effort (as depicted in the left waveform in Figure 3) and excessive respiratory muscle rest (as depicted in the middle waveform). The human data collected by Levine and co-workers (23), together with the animal data demonstrating ventilator-induced muscle injury (10), provide an added impetus for paying close attention to pressure waveforms. Although biologically plausible, the effect of waveform monitoring on patient outcome has not been tested.

Novel therapies may prove beneficial in preventing or reversing this injury. For example, a protease inhibitor, leupeptin, was recently shown to completely prevent atrophy of diaphragmatic fibers in rats that received controlled mechanical ventilation for 24 hours (35). Administration of leupeptin abolished the increased activity of 2 intracellular proteases calpain and cathepsin B induced by controlled mechanical ventilation (35). Likewise, the antioxidant Trolox (Hoffmann–La Roche, Basel, Switzerland) has been shown to retard proteolysis and prevent diaphragmatic contractile impairment in animals that receive controlled mechanical ventilation (36). Trials of such agents have not been undertaken in ventilated patients.

In conclusion, clinicians have long been aware that substantial lung injury results when a ventilator places too much stress on the pulmonary parenchyma. For more than 20 years, clinicians have known that patients can perform excessive respiratory muscle work while receiving mechanical ventilation if the mode and settings are not carefully selected. Increasing evidence now suggests that too little stress on the respiratory muscles may cause disuse atrophy and muscle damage. To navigate a patient’s safe passage between the Scylla of excessive patient effort and the Charybdis of excessive respiratory muscle rest, we suggest that clinicians carefully titrate ventilator settings and pay close attention to the contour of the airway pressure waveform.

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