Low-Tidal-Volume Ventilation in the Acute Respiratory Distress Syndrome

Atul Malhotra, M.D.

A 55-year-old man who is 178 cm tall and weighs 95 kg is hospitalized with community-acquired pneumonia and progressively severe dyspnea. His arterial oxygen saturation while breathing 100% oxygen through a face mask is 76%; a chest radiograph shows diffuse alveolar infiltrates with air bronchograms. He is intubated and receives mechanical ventilation; ventilator settings include a tidal volume of 1000 ml, a positive end-expiratory pressure (PEEP) of 5 cm of water, and a fraction of inspired oxygen (FiO₂) of 0.8. With these settings, peak airway pressure is 50 to 60 cm of water, plateau airway pressure is 38 cm of water, partial pressure of arterial oxygen is 120 mm Hg, partial pressure of carbon dioxide is 37 mm Hg, and arterial blood pH is 7.47. The diagnosis of the acute respiratory distress syndrome (ARDS) is made. An intensive care specialist evaluates the patient and recommends changing the current ventilator settings and implementing a low-tidal-volume ventilation strategy.

**THE CLINICAL PROBLEM**

Acute lung injury is defined by the American–European Consensus Conference as the acute onset of impaired gas exchange (the ratio of the partial pressure of arterial oxygen in millimeters of mercury to the FiO₂ of <300) and the presence of bilateral alveolar or interstitial infiltrates in the absence of congestive heart failure.¹ Acute lung injury has an incidence of 86 cases per 100,000 person-years and a mortality rate of 39%. In the United States, there are an estimated 190,600 cases annually, leading to 74,500 deaths and 3.6 million hospital days.² ARDS is a more severe form of lung injury, defined by a ratio of the partial pressure of arterial oxygen to FiO₂ of less than 200.¹ The incidence of ARDS is 64 cases per 100,000 person-years, and the mortality rate is 40 to 50%. Common causes of ARDS are sepsis (with or without a pulmonary source), trauma, aspiration, multiple blood transfusions, pancreatitis, inhalation injury, and certain types of drug toxicity.²³

**PATHOPHYSIOLOGICAL CHARACTERISTICS AND EFFECT OF THERAPY**

Acute lung injury can be defined physiologically as acute respiratory failure due to pulmonary edema in the absence of an elevation in the hydrostatic pressure in the pulmonary veins. The syndrome is characterized by diffuse alveolar damage associated with increased permeability of the alveolar–capillary membrane. Edema fluid and plasma proteins leak from the vasculature into the alveolar spaces. Macrophages and neutrophils accumulate in the interstitium, and proinflammatory cytokines are...
reduced to the lungs. Hyaline membranes form in the alveoli. The chemical composition and functional activity of surfactant can be altered in patients with ARDS, resulting in an elevation in surface tension, which tends to promote regional alveolar collapse. The efficiency of gas exchange deteriorates precipitously.

Endotracheal intubation and mechanical ventilation are almost always necessary to manage the severe hypoxemia of ARDS. In the past, the primary goal of ventilation had been to increase arterial oxygenation to an acceptable range (principally, an arterial oxyhemoglobin saturation of 88 to 95%, but also normal partial pressure of carbon dioxide and pH). This objective was usually met with the use of a high FiO₂ and a high minute ventilation. Tidal volumes were correspondingly high. Although the practice was variable, tidal volumes of 10 to 15 ml per kilogram of body weight (as compared with a normal tidal volume of 5 to 7 ml per kilogram for spontaneously breathing controls at rest) were commonly used. The concept of "recruitment" (i.e., the opening of previously collapsed alveoli) was thought to provide a justification for such high-volume ventilation.

More recently, it has been recognized that mechanical ventilation, although potentially lifesaving, can contribute to the worsening of lung injury. This phenomenon is called ventilator-induced lung injury (Fig. 1). The volume of aerated lung in patients with ARDS is considerably reduced because of edema and atelectasis. As a result, ventilation with the use of high tidal volumes may cause hyperinflation of relatively normal regions of aerated lung. Since nonaerated lung tissue is stiffer than normal lung tissue, compliance is reduced and airway pressure is increased. Excessive volume and pressure, with correspondingly high transpulmonary pressure (the difference in pressure between the airway and the pleural space), contribute to ventilator-induced lung injury. In addition, the inflation of normal alveoli adjacent to noninflated, abnormal alveoli may create high shear forces that can contribute to injury of the lung parenchyma, even at modest applied pressures. The consequences of lung overdistention include direct physical damage, with disruption of the alveolar epithelium and capillary endothelium, as well as the induction of an inflammatory response, with the release of cytokines and other mediators. Some evidence suggests that the inflammatory response induced during ventilator-induced lung injury has systemic consequences, contributing to the pathogenesis of multisystem organ failure in patients with ARDS.

In 1993, a consensus conference of the American College of Chest Physicians recommended that applied tidal volume be decreased in patients with ARDS who had a plateau pressure of 35 cm of water or more, even though such a decrease can cause some degree of hypercapnia (sometimes referred to as permissive hypercapnia). This recommendation was based largely on data from studies of animals, since at that time there were few clinical studies of low-tidal-volume ventilation and no definitive data showing an outcome benefit with this approach. The use of PEEP was endorsed as a means of supporting oxygenation, but it was also noted that excessive PEEP may be associated with deleterious effects; the role and optimal use of PEEP in a low-tidal-volume ventilation strategy was not specified, owing to the lack of clinical-trial data addressing this issue.

**Figure 1. Normal Rat Lungs and Rat Lungs after Receiving High-Pressure Mechanical Ventilation at a Peak Airway Pressure of 45 cm of Water.**

After 5 minutes of ventilation, focal zones of atelectasis were evident, in particular at the left lung apex. After 20 minutes of ventilation, the lungs were markedly enlarged and congested; edema fluid filled the tracheal cannula. Adapted from Dreyfuss et al. with the permission of the publisher.

**Clinical Evidence**

The first major randomized clinical trial to provide direct evidence of a potential benefit of low-tidal-volume ventilation in patients with ARDS was published in 1998. Amato et al. compared conventional ventilation with a low-tidal-volume, "pro-
tective ventilation” strategy in 53 patients (Fig. 2). Conventional ventilation involved a tidal volume of 12 ml per kilogram of body weight, a low PEEP, and a partial pressure of carbon dioxide of 35 to 38 mm Hg. Protective ventilation involved a tidal volume at or below 6 ml per kilogram, a high PEEP, and permissive hypercapnia. The mortality rate at 28 days was significantly lower with protective ventilation than with conventional ventilation (38% vs. 71%). There was also significantly less clinical barotrauma and a significantly higher rate of weaning from ventilation in the protective-ventilation group. Although some criticized this study for the high mortality rate in the conventional-ventilation group, the patients studied were extremely ill (with failure of a mean of 3.6 organs per patient).

In a subsequent, larger study by the Acute Respiratory Distress Syndrome Network (ARDSNet), 861 patients with acute lung injury or ARDS were randomly assigned to receive ventilatory support involving a tidal volume of either 12 or 6 ml per kilogram of predicted body weight. Although tidal volume was the manipulated variable, a major goal of the ventilatory strategy was to keep the plateau airway pressure below 30 cm of water; therefore, the group that underwent ventilation at 6 ml per kilogram of predicted body weight is often referred to as the low-stretch group. The low-stretch strategy was associated with a significantly lower mortality rate (31%, vs. 40% with ventilation at 12 ml per kilogram of predicted body weight). Therefore, the best available evidence is for a ventilation strategy using a tidal volume of 6 ml per kilogram of predicted body weight for patients with acute lung injury or ARDS.

Three other small, randomized trials, performed during the same period, failed to demon-
strate a benefit of low-tidal-volume ventilation in patients with acute lung injury or ARDS. The reasons for this apparent inconsistency in study results are not clear, but they may have included differences in the airway pressures required for conventional ventilation in each trial. A significant survival benefit has been shown in trials in which conventional ventilation was associated with marked elevations in airway pressures. This finding suggests that the benefit of low-tidal-volume ventilation is a function of plateau pressure. However, the relationship between plateau pressure and risk of injury from ventilation may be continuous, since subsequent data have failed to confirm the concept of a threshold below which airway pressure is no longer injurious. Furthermore, evidence of hyperinflation may occur at a low volume or pressure, depending on the amounts of poorly aerated and nonaerated lung tissue. In addition, theoretically, as described above, high shear forces can create injury at junctions of normal and abnormal lung tissue, even when the applied pressures are below 30 cm of water.

CLINICAL USE

Low-tidal-volume ventilation should be implemented in the context of a broader strategy of critical care management in a patient with acute lung injury or ARDS. An initial tidal volume of 6 ml per kilogram of predicted, not actual, body weight should be used, as in the ARDSNet trial. The predicted body weight (PBW) is calculated as follows: for men, PBW = 50.0 + 0.91 (height in centimeters – 152.4); and for women, PBW = 45.5 + 0.91 (height in centimeters – 152.4).

The concept underlying this approach is that it normalizes the tidal volume to lung size, since lung size has been shown to depend most strongly on height and sex. For example, a person who ideally weighs 70 kg and who then gains 35 kg has essentially the same lung size as he or she did when at a weight of 70 kg and should not receive ventilation with a higher tidal volume just because of the weight gain.

The initial respiratory rate should be set in the range of 18 to 22 breaths per minute. This is a somewhat higher rate than is used in other ventilatory schemes; it is intended to maintain a minute ventilation that is high enough to avoid marked hypercapnia. However, some degree of hypercapnia is to be expected with low-tidal-volume ventilation. Ideally, the partial pressure of carbon dioxide should rise gradually to prevent acute acidemia and to ensure hemodynamic stability. Specific target values of partial pressure of carbon dioxide and pH are debatable, although some clinicians would argue to keep the current guidelines of a partial pressure of carbon dioxide of less than 80 mm Hg and a pH of greater than 7.20. Although the administration of sodium bicarbonate has sometimes been advocated to maintain an acceptable pH, this is controversial in theory and rarely necessary in practice. In fact, mean partial pressures of carbon dioxide below 50 mm Hg were usually achieved in the ARDSNet study in the low-stretch group.

The response to low-tidal-volume ventilation should be assessed initially on the basis of plateau airway pressure. The goal should be to maintain a plateau airway pressure (i.e., the pressure during an end-inspiratory pause) of 30 cm of water or less; if this target is exceeded, the tidal volume should be further reduced to a minimum of 4 ml per kilogram of predicted body weight. An important caveat relates to patients who have stiff chest walls (for example, those with massive ascites). In such patients, it is reasonable to allow the plateau pressure to increase to values greater than 30 cm of water, since the pleural pressures are elevated and hence the transpulmonary pressures are not elevated (i.e., there is not necessarily alveolar overdistention). Whether the tidal volume should be increased in the patient with a plateau pressure substantially lower than 30 cm of water is less clear; given the lack of evidence of a safe threshold, some experts would argue that the lower the plateau pressure, the better, provided that the patient is comfortable and that gas-exchange goals are reached.

The optimal FiO2 also requires consideration in the context of low-stretch ventilation. Since severe hypoxemia is a characteristic feature of ARDS, efforts to improve oxygenation and to achieve a target arterial oxyhemoglobin saturation of about 90% may initially require high FiO2 levels. However, the prolonged use of high FiO2 levels can theoretically increase the risk of oxygen toxicity, which may actually increase injury to the lung parenchyma. Therefore, other adjustments may be necessary to improve oxygenation while reducing the FiO2. One approach is to use PEEP to increase oxygenation, although this should be done while plateau airway pressure is monitored. In the
ARDSNet trial, combinations of FiO\textsubscript{2} and PEEP values were specified for both study groups according to predefined settings (Table 1). However, the level of oxygenation is a poor predictor of outcome. In the ARDSNet trial, oxygenation was worse in the low-stretch group, despite a reduced mortality rate. Therefore, some experts recommend the application of PEEP based on lung mechanics rather than gas exchange (see below).

Alternatives to low-tidal-volume ventilation either have been unsuccessful (e.g., partial liquid ventilation\textsuperscript{26}) or are unproven (e.g., high-frequency oscillation\textsuperscript{27,28}). However, many unproven strategies, such as open-lung protective ventilation or prone positioning, may be useful in combination with low-tidal-volume ventilation\textsuperscript{29,30} and thus should not be considered to be competing therapies.

### A D V E R S E  E F F E C T S

Low-tidal-volume ventilation can result in an increase in the partial pressure of carbon dioxide to above the normal range (permissive hypercapnia). As noted above, permissive hypercapnia results in respiratory acidosis, which can be mitigated to some degree by means of increasing the respiratory rate and gradual renal buffering. Potentially harmful consequences of permissive hypercapnia include pulmonary vasoconstriction and pulmonary hypertension, proarrhythmic effects of increased discharge of the sympathetic nervous system, and cerebral vasodilation yielding increased intracranial pressure. However, experimental data have suggested that permissive hypercapnia is not only safe but potentially beneficial.\textsuperscript{31} In most cases, hemodynamic characteristics actually improve owing to the release of catecholamines.\textsuperscript{32} Nonetheless, permissive hypercapnia should probably be used with caution in patients with heart disease and is relatively contraindicated in those with elevated intracranial pressure.

For at least some patients, low-tidal-volume ventilation is associated with a sensation of dyspnea that is uncomfortable and poorly tolerated.\textsuperscript{33} Such patients may require substantial sedation to maintain patient–ventilator synchrony, although sedation requirements were equivalent in patients receiving ventilation with a low tidal volume and those receiving ventilation with a high tidal volume in the ARDSNet trial.\textsuperscript{34} If discomfort is an issue, either minor elevations in delivered tidal volume can be made or sedation can be increased. Sedation can generally be managed with the use of short-acting agents like propofol and with daily interruptions to determine whether the requirement for sedation is ongoing.\textsuperscript{35,36}

### A R E A S  O F  U N C E R T A I N T Y

As noted above, PEEP is commonly adjusted in accordance with FiO\textsubscript{2} in low-stretch ventilation, as was systematically defined in the ARDSNet trial. Whether high levels of PEEP may be beneficial in this setting has not been clearly established. PEEP can prevent the collapse of small airways and alveoli (referred to as derecruitment), further improving oxygenation and ventilation–perfusion matching. High PEEP values may also minimize a phenomenon called “atelectrauma,” which is the repetitive opening and closing of alveoli, with the propensity for collapse owing to either surfactant dysfunction resulting in high surface tension or elevated pleural pressures that promote regional lung collapse.\textsuperscript{37} Results of trials evaluating the role of a high PEEP have been inconsistent with regard to its potential benefit.\textsuperscript{17,29,38,39} At the bedside, the PEEP can often be adjusted on the basis of responses in individual patients. For example, recruitment can be inferred if the plateau pressure does not rise substantially after the PEEP is increased while the tidal volume remains fixed. In contrast, a rise in plateau pressure that is equal
to or greater than the increase in PEEP would suggest that recruitment has not occurred and possibly that there is overdistention or regional hyperinflation. In the patient in whom there is recruitment, sustained high-pressure inflations (referred to as recruitment maneuvers), followed by the administration of a high PEEP and a low tidal volume, may reduce lung injury from shear forces by promoting homogeneity of inflation within the lung (Fig. 3). However, this approach, which has been designated “open-lung protective ventilation,” remains unproved in clinical trials.

Patients who do not have acute lung injury or ARDS may also benefit from the limiting of lung stretch. Some observational data provide support for the concept that inappropriate ventilator settings may contribute to the development of ARDS. That is, ARDS may be iatrogenic in some cases. In addition, because of the occasional failure to diagnose and appropriately manage acute lung injury or ARDS once it develops, some have made the argument to limit lung stretch in all patients undergoing mechanical ventilation, including during the perioperative period. However, there have been few randomized trials in this area.

**GUIDELINES**

As noted above, a consensus conference of the American College of Chest Physicians recommended in 1993 that low-tidal-volume ventilation be used in patients with ARDS. No subsequent formal guidelines dealing with low-tidal-volume ventilation have been developed by the American College of Chest Physicians, the American Thoracic Society, or the Society of Critical Care Medicine. However, all three organizations endorsed a set of industry-funded guidelines, called the Surviving Sepsis Campaign, published in 2004. The process by which these guidelines were developed has

![Figure 3. Effects of Recruitment Maneuvers to Promote Homogeneity within the Lung.](image)

Panels A through D show the progressive resolution of infiltrates after application of inflations of increasing pressure. Reprinted from Borges et al.
been criticized, although the recommendations with regard to mechanical ventilation are generally accepted.

The Surviving Sepsis guidelines endorse low-tidal-volume ventilation (6 ml per kilogram of predicted body weight), with a goal of maintaining end-inspiratory plateaux pressures of less than 30 cm of water. Hypercapnia is deemed acceptable in this context, in the absence of increased intracranial pressure. The use of PEEP is recommended to prevent alveolar collapse at the end of expiration and to maintain adequate oxygenation.

**RECOMMENDATIONS**

The patient described in the vignette is an appropriate candidate for low-tidal-volume ventilation, given the diagnosis of ARDS and the high plateau airway pressure attained with the use of conventional mechanical ventilation. The tidal volume should be reduced to 6 ml per kilogram of predicted body weight, according to the ARDSNet formula (resulting in a tidal volume of 440 ml for this patient). I would then increase the ventilatory rate to 20 breaths per minute and observe the resulting plateau pressure and arterial blood gas levels, making subsequent adjustments as appropriate. For a patient with a plateau pressure above 30 cm of water, I would reduce the tidal volume further, by 1 ml per kilogram of predicted body weight, and I would then remeasure the plateau pressure. For a patient with an arterial oxyhemoglobin saturation below 88 to 90%, I would attempt to increase the PEEP to improve oxygenation without exceeding the target plateau pressure. Depending on the individual case, I will often attempt to perform a recruitment maneuver (sustained high-pressure inflation under heavy sedation and adequate fluid resuscitation) and then attempt to maintain recruitment by applying increased levels of PEEP and observing the resulting change in plateau pressure.

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Acute neuromuscular weakness in the intensive care unit

Bobby Varkey Maramattom, MD, DM; Eelco F. M. Wijdicks, MD

**Introduction:** Patients in the intensive care unit develop generalized weakness due to a number of factors. Neuromuscular weakness is a common cause of failure to wean from the ventilator and decreased limb movements. A rational approach to evaluation of weakness will help to identify most of the common causes of neuromuscular weakness in the intensive care unit.

**Aims:** This review provides an analysis of neuromuscular weakness and a practical algorithm to assist in diagnostic evaluation.

**Conclusions:** The most common acquired causes of weakness in the critically ill patient in the intensive care unit are critical illness polyneuropathy and critical illness myopathy. In the intensive care unit setting, electrophysiological studies, biopsies, and imaging studies are often necessary to complement the clinical impression. (Crit Care Med 2006; 34:2835–2841)

**Key Words:** diagnosis; intensive care unit; outcome sepsis; treatment; weakness

Sick patients can be weak, but only a proportion of these individuals develop a neurologic disorder causing muscle weakness. However, critically ill patients are exposed to multiple stressors, fluid and electrolyte changes, catabolic stresses, nutritional deficiencies, and medications that act in combination to produce damage to the motor unit. Thus, critically ill patients have a higher likelihood of acquiring neuromuscular weakness in the intensive care unit (ICU). In addition to prolonging hospital stay and increasing morbidity and mortality, these disorders also inflate hospital costs by of thousands of dollars (1).

The spectrum of neuromuscular disease that is encountered in today’s ICU has evolved over the last few decades. Nowadays, weakness acquired in the ICU due to critical illness myopathy (CIM) or polynuropathy (CIP) is two to three times more common than primary neuromuscular disorders such as Guillain-Barré syndrome (GBS), myopathies, or motor neuron diseases (2).

Patients in the ICU can develop a variety of mononeuropathies or plexopathies related to ischemia, pressure palsies, prolonged recumbency, compartment syndromes, hematomas, or other causes. They can also develop weakness due to intracranial processes such as ischemic stroke or other diseases. The discussion of these focal or central causes of weakness in ICU patients is also outside the scope of this review. Nevertheless, a brief mention will be made of some of these conditions because a review of weakness in the ICU will be incomplete if these entities are omitted.

To be fair to the title, this review will, however, focus on patients with generalized neuromuscular weakness in the ICU. Two clinical presentations are encountered among this group. One group is those patients who are admitted to the ICU with a nonneurologic illness and subsequently are detected to have generalized weakness in the ICU. The other group of patients is those in whom catastrophic weakness and respiratory failure necessitate emergent admission to the ICU. In these cases, diagnostic tests are usually postponed until the patient is stabilized.

Although a good history and examination help in identifying and localizing the weakness, there are a number of confounding factors. Patients in the ICU are often confused, sedated, or intubated and may find it difficult to communicate with the clinician. Weakness is often detected incidentally or during attempts to wean, and the exact onset of weakness is often unclear. Examination is also hampered by indwelling intravascular catheters, restraints, and sedatives. Nevertheless, important clues can be obtained from the history, examination, scrutiny of medication charts, and investigation reports. Particular attention should be paid to the use of neuromuscular blockers, steroids, antiretroviral agents (3), statins (4, 5), and fibrates (6) (Table 1). The cumulative drug dosage; adjustment for renal, hepatic, and organ failure; and drug interactions should be analyzed. The identification of the level of pathology will help guide further investigations.

**EVALUATION OF THE ICU PATIENT WITH NEUROMUSCULAR WEAKNESS**

Important components of history are outlined in Table 2. Clinical examination also provides invaluable clues. Specific findings that should be elicited include muscle wasting or swelling, muscle tenderness, fasciculations or myokymia, myotonia, presence of tendon reflexes, and skin lesions. Fasciculations are random single muscle fiber twitches visible in superficial muscles, especially over the limbs. The phenomenon of myokymia refers to an undulating rippling movement of muscle fibers beneath the skin that mimics a wriggling worm (7). Myotonia is a delayed relaxation of muscle after voluntary contraction (action myotonia) or mechanical stimulation (percussion myotonia) (8). Facilitation of sluggish reflexes after repetitive tendon taps or brief isometric exercise is a clue to the Lambert-Eaton syndrome. Important skin lesions such as the heliotrope rash of dermatomyositis, purpura, telangi-
Table 1. Drugs and their effects on the neuromuscular system

<table>
<thead>
<tr>
<th>Common Drugs Affecting Neuromuscular Function</th>
<th>Mechanism of Action</th>
<th>Clinical Manifestation</th>
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<tbody>
<tr>
<td>D-penicillamine</td>
<td>Impairment of neuromuscular transmission</td>
<td>Myasthenia-like syndrome</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>Impairment of neuromuscular transmission</td>
<td>Myasthenia-like syndrome</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Impairment of neuromuscular transmission</td>
<td>Myasthenia-like syndrome</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Impairment of neuromuscular transmission</td>
<td>Myasthenia-like syndrome</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Impairment of neuromuscular transmission</td>
<td>Myasthenia-like syndrome</td>
</tr>
<tr>
<td>Magnesium containing laxatives</td>
<td>Impairment of neuromuscular transmission</td>
<td>Myasthenia-like syndrome</td>
</tr>
<tr>
<td>Lithium</td>
<td>Impairment of neuromuscular transmission</td>
<td>Myasthenia-like syndrome</td>
</tr>
<tr>
<td>Statins</td>
<td>Interaction with cytochrome P-450 system</td>
<td>Necrotizing myopathy</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Interaction with cytochrome P-450 system</td>
<td>Necrotizing myopathy</td>
</tr>
<tr>
<td>D-penicillamine</td>
<td>Interaction with cytochrome P-450 system</td>
<td>Necrotizing myopathy</td>
</tr>
<tr>
<td>Zidovudine, stavudine, lamivudine</td>
<td>Interaction with cytochrome P-450 system</td>
<td>Necrotizing myopathy</td>
</tr>
</tbody>
</table>

Table 2. Clues toward specific disorders producing neuromuscular weakness

| Critical illness, sepsis, multiple organ dysfunction syndrome | Critical illness myopathy |
| Skin rash | Dermatomyositis, vasculitis |
| Fluctuating weakness, ptosis, coexistent autoimmune conditions | Myasthenia gravis |
| Aminoglycoside use | Antibiotic induced myasthenia |
| Family history, episodic crises, infantile onset | Congenital myasthenic syndromes |
| Antecedent infections, vaccinations, diarrhea, upper respiratory tract infections, sensory-motor symptoms | Guillain-Barré syndrome, CIDP |
| Episodic abdominal crises, psychiatric illness, dysautonomia, seizures, encephalopathy | Porphyria |
| Trauma, crush injuries, renal failure | Rhombomysolysis, phrenic nerve injuries |
| History of mosquito bites, fever, asymmetric flaccid weakness, encephalopathy | West Nile virus infection |
| Family history, retinitis pigmentosa, mental retardation, seizures, deafness, progressive myoclonic epilepsy | Mitochondrial myopathy |

CIDP, chronic inflammatory demyelinating polyneuropathy.

Table 3. Mnemonic for differential diagnosis of generalized weakness in the intensive care unit

| M | Medications: steroids, neuromuscular blockers (pancuronium, vecuronium), zidovudine, amiodarone |
| U | Undiagnosed neuromuscular disorder: myasthenia, LEMS, inflammatory myopathies, mitochondrial myopathy, acid maltase deficiency |
| S | Spinal cord disease (ischemia, compression, trauma, vasculitis, demyelination) |
| C | Critical illness myopathy, polyneuropathy |
| L | Loss of muscle mass (cachectic myopathy, rhabdomyolysis) |
| E | Electolyte disorders (hypokalemia, hypophosphatemia, hypermagnesemia) |
| S | Systemic illness (porphyria, AIDS, vasculitis, paraneoplastic, toxic) |

LEMS, Lambert-Eaton myasthenic syndrome; AIDS, acquired immunodeficiency syndrome.
locked-in state will direct the further line of investigations. Computed tomography scans or MRI will identify most of the central nervous system lesions responsible for this state.

**Spinal Cord Disorders.** The most common noncompressive myelopathy causing quadriparesis is transverse myelitis or myelopathy. Transverse myelitis or myelopathy is most often idiopathic or postinfectious but can also be due to infectious myelitis caused by viruses such as Coxsackievirus, herpes, or cytomegalovirus or bacteria including Mycoplasma or Legionella as well as multiple sclerosis, Devic’s disease, collagen vascular diseases, or spinal cord infarction (14).

Spinal cord infarction is a known complication of aortic dissection, acute aorto-iliac occlusion, and thoracoabdominal aortic surgeries. Spinal cord infarction can also occur after cardiac arrest and global hypotension. In such cases there is a predilection for the lumbar sacral cord to be involved (15). Such patients can potentially suffer a “double hit” with cortical watershed infarctions producing brachial paresis and spinal cord infarction resulting in paraplegia. Unexplained hypotension or bradycardia in an unconscious trauma patient should prompt evaluation of spinal cord injury with a whole-spine MRI if possible. MRI adequately delineates most myelopathies that produce generalized weakness.

Patients present with acute flaccid areflexic weakness that mimics GBS during the stage of spinal shock. Clinical clues such as early bowel or bladder dysfunction, a sensory level, neck pain, or impalpable lower limb pulses should alert the clinician to a myelopathy and the need for a spinal MRI. Transverse myelitis may respond to high-dose intravenous methylprednisolone and should be identified early (16). Spinal cord infarction has no specific therapy and patients usually receive only supportive care. Infectious myelitis is treated with the appropriate antiviral or antibiotic regimen.

**Anterior Horn Cell Disorders.** Although acute poliomyelitis due to poliovirus has nearly been eradicated, there are a number of viral mimics of acute poliomyelitis (17). Notable among this is the West Nile virus (WNV), which is known to produce a meningo-encephalitis with an acute flaccid paralysis (18). Severe WNV infection can also mimic GBS but is differentiated by fever; encephalopathy; predominantly proximal, asymmetric weakness; axonal pathology.

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**Figure 1.** Algorithm for evaluation of generalized weakness in the intensive care unit (ICU). CK, creatine kinase; ESR, erythrocyte sedimentation rate; ABG, arterial blood gas; MRI, magnetic resonance imaging; Rx, prescription; EMG, electromyograph; AIDP, acute inflammatory demyelinating polyneuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; CIP, critical illness polyneuropathy; RNS, repetitive nerve stimulation.

**Table 4. Relevant lab investigations in the diagnosis of neuromuscular weakness**

<table>
<thead>
<tr>
<th>Hemogram</th>
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<tbody>
<tr>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>Electrolytes: sodium, potassium, calcium, phosphorus, magnesium</td>
</tr>
<tr>
<td>Muscle enzymes</td>
</tr>
<tr>
<td>Creatine kinase</td>
</tr>
<tr>
<td>Serum lactate levels</td>
</tr>
<tr>
<td>Autoantibody panel</td>
</tr>
<tr>
<td>Anti-Jo1 antibodies, antibodies to the PM-Scl nucleolar antigen complex, acetylcholine receptor antibodies, anti-MuSK antibodies, anti-voltage gated calcium channel antibodies</td>
</tr>
<tr>
<td>Electrophysiological studies</td>
</tr>
<tr>
<td>Nerve conduction study including phrenic nerve study, electromyography including respiratory, diaphragmatic muscles, repetitive nerve stimulation, single fiber EMG</td>
</tr>
<tr>
<td>CSF examination</td>
</tr>
<tr>
<td>To look for albuminocytological dissociation, pleocytosis, malignant cells or cultures</td>
</tr>
<tr>
<td>MRI imaging of brain and spine with gadolinium</td>
</tr>
<tr>
<td>Muscle and nerve biopsy, with overlying skin</td>
</tr>
<tr>
<td>Chest radiograph/CT chest to look for contributory parenchymal lung diseases as well as thymoma, other neoplastic conditions</td>
</tr>
</tbody>
</table>

PM-Scl, polymyositis/scleroderma; MuSK, muscle-specific receptor tyrosine kinase; EMG, electromyogram; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; CT, computed tomography.
on nerve conduction studies (19); and cerebrospinal fluid variables. The cerebrospinal fluid typically shows lymphocytic pleocytosis with elevated proteins. Enzyme-linked immunosorbent assay for immunoglobulin (Ig)M antibody to WNV is highly sensitive and should be considered. As IgM antibodies can persist for up to a year after primary infection, serial IgM titers or IgG avidity studies can help to differentiate primary infection from past infection (20). MRI may show enhancement of the cauda equina, spinal cord signal changes, and cerebral parenchymal or leptomeningeal signal changes (21). Treatment is mainly supportive, and no antiviral medications have any proven benefit in the management of WNV.

Of the other anterior horn cell disorders, amyotrophic lateral sclerosis is well known to present with respiratory failure due to primary involvement of the phrenic motor neurons (22). The diagnosis is usually clear-cut on electrophysiological studies, and widespread denervation is seen on electromyogram. Although paraneoplastic motor neuron disorders can present with rapidly evolving respiratory weakness, they are uncommon (23).

**Polyneuropathies.** The most common variety of polyneuropathy encountered in the ICU nowadays is CIP (24) followed by CIM. Sepsis, systemic inflammatory response syndrome (SIRS), and multiple organ dysfunction syndrome are important in the development of these syndromes although additional factors such as use of NM blocking agents, corticosteroids, cytotoxic drugs, and status asthmaticus have also been identified in the development of CIP/CIM (25–29). Together, these disorders are encountered in about 30–60% of ICU patients (30–32). CIM may be the more common of the two disorders in ICU patients. CIP may occur as early as 2–5 days in the presence of sepsis or SIRS, but most often it takes ≥1 wk of mechanical ventilation before these syndromes develop (30, 32). One of the reasons for the delay is that most patients with SIRS or sepsis either have an underlying encephalopathy (“septic encephalopathy”) or are administered neuromuscular blocking agents or sedatives around the clock to facilitate mechanical ventilation.

The first neurologic consultation is requested when the critical care team finds it difficult to wean the patient from the ventilator and lung, chest wall, or cardiac causes of failure to wean have been excluded. The typical CIM/CIP patient has a flaccid quadriplegia and is often areflexic or hyporeflexic. Cranial nerves are often spared. Sensory examination is often difficult in these patients, and the differentiation between CIP and CIM often rests on electrophysiology. Compound muscle action potential amplitudes are reduced in both conditions; however, sensory nerve action potentials amplitudes are normal in CIM and reduced or absent in CIM. Phrenic nerve studies and needle electromyogram of the respiratory muscles can also establish CIM/CIP as the cause of failure to wean from the ventilator.

A number of terminologies such as acute quadruplegic myopathy, critical care myopathy, acute necrotizing myopathy of intensive care, thick filament myopathy, acute corticosteroid myopathy, acute myopathy in severe asthma, and acute pancuronium-associated myopathy have been used to allude to CIM. “Lumpers” prefer to term them all “CIM” and “splitters” prefer to subclassify CIM. Histopathologically, four subtypes of CIM have been identified on muscle biopsy—the necrotizing, cachectic, acute rhabdomyolysis, and the thick filament (myosin) loss type (30, 33–35). Histopathologic subtyping greatly influences the prognostic outcome of CIM as muscle recovery is poor in the necrotizing variant and relatively better in the other subtypes.

Muscle biopsies demonstrate characteristic features of muscle necrosis or selective loss of thick (myosin) myofilaments with preservation of thin (actin) myofilaments and Z discs without muscle necrosis in the thick filament loss type of CIM (35). Creatine kinase levels are elevated in about 50% of patients with CIM if estimated early in the illness. Treatment of these syndromes is mainly supportive and rests on aggressive management of the underlying sepsis/SIRS. Fluid resuscitation, antibiotic therapy, surgical drainage of abscesses, and physiotherapy all have a role. Intravenous immunoglobulin has thus far not been promising in patients with CIP (36). The long-term outcome following CIP/CIM ultimately depends on the underlying illness. If these are surmountable (the median hospital stay in patients with CIP is around 3 months), recovery from CIP can be surprisingly good; however, the outcome following CIM can be poor particularly in the necrotizing variants (37, 38).

Patients with GBS present with an ascending paralysis with respiratory and cranial nerve involvement and diffuse areflexia or hyporeflexia. Most patients show features of demyelination on nerve conduction studies and show a good response to intravenous immunoglobulin (IgIV) or plasma exchange. A proportion of patients develop regional variants of GBS or an axonal form of GBS, which may have a poorer prognosis (the acute motor axonal neuropathy or acute motor sensory axonal neuropathy variants). The clinical features of GBS are quite distinct from CIM/CIP and include weakness developing before ICU admission, history of a preceding upper respiratory or diarrheal illness, conspicuous cranial nerve involvement, albumino-cytological dissociation on cerebrospinal fluid examination, and demyelinating features on nerve conduction studies (24). Some patients have a documented prior infection with certain serotypes of *Campylobacter jejuni* that evoke antiganglioside antibodies against the nodes of Ranvier (39). Moreover, CIP occurs on the background of...
sepsis and SIRS in a patient who is being mechanically ventilating rather than developing *de novo*. A peculiar situation arises when patients with demyelinating variants of GBS develop sepsis or SIRS and resultant worsening of their neuropathy. Repeat electrophysiologic studies may show axonal degeneration. In such a situation, superadded CIP may be a more likely cause of worsening than axonal GBS (30). In this case, treatment and management of sepsis and SIRS should take precedence over repeat IgIV or plasma exchange.

Other hospital-acquired polyneuropathies are rare but include acute vasculitic neuropathies, acute porphyria, drug-induced neuropathies, and the AIDS-associated cytomegalovirus polyradiculoneuropathy (Table 5).

**Neuromuscular Junction Disorders.** Common myasthenic syndromes encountered in the ICU include myasthenia gravis, Lambert-Eaton myasthenic syndrome, prolonged neuromuscular blockade, and anti-biotic-induced myasthenia. Oculobulbar involvement should raise the suspicion of myasthenia gravis and prompt a request for repetitive nerve stimulation studies and assessment of acetyl choline receptor antibody titers. Patients with myasthenia gravis can present in a crises with profound worsening of respiratory or other muscles. Common precipitants of crises include intercurrent infections, administration of drugs that impair neuromuscular junction transmission (Table 1), myasthenic crises (undermedication), or cholinergic crises (overmedication). Although it is often difficult to distinguish between myasthenic and cholinergic crises, fasciculations, miosis, hypersalivation, lacrimation, diarrhea, and emesis are more suggestive of overmedication (cholinergic crises). To complicate matters, a poor response or even a “hypersensitivity” to anticholinesterase agents is observed in some “seronegative” myasthenic patients who are positive for antibodies to muscle-specific receptor tyrosine kinase (40). Hypersensitivity is manifested by severe muscle fasciculations in the facial muscles, blurring of vision, sialorrhea, and abdominal cramping mimicking a cholinergic crises (41). These patients may respond only to plasma exchange during their episodes of crises (42).

IgIV and plasma exchange are often used as rescue therapies in myasthenic patients with crises (43). Steroids, immunosuppressive medications, and thymectomy are alternative options in the long-term management of myasthenia gravis.

### Table 5. Common neuromuscular conditions presenting with generalized weakness in the intensive care unit

<table>
<thead>
<tr>
<th>Muscle diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical illness myopathy</td>
</tr>
<tr>
<td>Inflammatory myopathies: polymyositis, dermatomyositis</td>
</tr>
<tr>
<td>Hypokalemic myopathy</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Muscular dystrophies</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
</tr>
<tr>
<td>Mitochondrial myopathies</td>
</tr>
<tr>
<td>Acid maltase deficiency</td>
</tr>
</tbody>
</table>

**Neuromuscular junction disorders**

- Myasthenia gravis
- Neuromuscular blocking agent induced weakness
- Antibiotic induced myasthenia
- Organophosphorus poisoning
- Snake bite
- Insect/marine toxins
- Lambert-Eaton myasthenic syndrome
- Congenital myasthenic syndromes
- Hypermagnessemia
- Botulism
- Tick paralysis

**Peripheral neuropathies**

- Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy)
- Chronic idiopathic demyelinating polyneuropathy
- Critical illness polyneuropathy
- Phrenic neuropathies
- Toxic neuropathy
- Vasculitic neuropathy
- Porphyric neuropathy
- Diphtheria
- Lymphoma
- Cytomegalovirus-related polyradiculoneuropathy

**Anterior horn cell disorders**

- Amyotrophic lateral sclerosis
- Paraneoplastic motor neuron disease
- West Nile virus infection
- Acute poliomyelitis
- Spinal muscular atrophy

**Spinal cord disorders**

- Trauma
- Hematoma
- Spinal cord infarction
- Epidural abscess
- Demyelination: multiple sclerosis, Devic’s disease, acute disseminated encephalomyelitis, transverse myelitis
- Infective myelitis: Cossackievirus A, B, cytomegalovirus, *Mycoplasma, Legionella, herpes*
- Paralytic rabies (“dumb rabies”)

High-rate repetitive nerve stimulation studies and assessment of antivoltage gated calcium channel antibodies should be ordered if Lambert-Eaton myasthenic syndrome is suspected. Lambert-Eaton myasthenic syndrome responds variably to 3,4-diaminopyridine or IgIV (44).

Competitive nondepolarizing neuromuscular blockers (NMB) are used in ICU patients to facilitate mechanical ventilation. All of these NMBs, including older amino steroids (pancuronium and vecuronium) and the newer benzylisoquinolinium NMBs such as atracurium (45), cisatracurium (46), and doxacurium, can induce prolonged NM blockade in ICU patients. NM blockade is also prolonged by metabolic acidosis and dyselectrolemia such as hypokalemia. NMBs also act synergistically with sepsis and SIRS in the pathogenesis of CIP and CIM.

Uncommon neuromuscular junction disorders seen in the ICU include botulism, tick paralysis, and hypermagnessemia. Botulism involves autonomic functions in addition to producing flaccid paralysis and areflexia. Hence patients often have internal and external ophthalmoplegia, dry mouth, and a paralytic ileus. Repetitive nerve stimulation studies may show features of presynaptic blockade. *Clostridium botulinum* or its toxin can be detected in stool, serum, wound cultures, or food samples by cultures or mouse bioassays. However, these are cumbersome procedures and not widely
Available. Although the mainstay of treatment is mechanical ventilation, it is imperative that the disease be diagnosed early to ensure that trivalent antitoxin is administered before the toxin binds to presynaptic nerve terminals. If administered early enough, the antitoxin reduces the mortality, morbidity, and length of hospital stay associated with botulism (47). Tick paralysis is found mostly in North America and Australia. It mimics GBS with an ascending motor paralysis, preserved sensations, and areflexia. Complete ophthalmoplegia provides a clue toward tick paralysis. Careful search and removal of the tick, which may be embedded in scalp hair, can result in rapid resolution of the paralysis. Hypermagnesemia mimics Lambert-Eaton myasthenic syndrome with respiratory failure, generalized weakness, and diminished reflexes (48). It is seen more often in patients with renal failure who consume magnesium-containing laxatives or antacids or eclamptic patients who are administered magnesium sulfate.

**Myopathies.** Among myopathies, the most common variety to be encountered in the ICU is probably CIM. Among other acquired myopathies, inflammatory myopathies deserve a special mention, of which two types are encountered frequently in the ICU: dermatomyositis and polymyositis. Dermatomyositis has a more malignant course than polymyositis and is easier to recognize by virtue of its characteristic skin rash. The rash is often erythematous, peri-orbital, and purplish (heliotrepe) and may spread into the neck and back in a “shawl” sign. It can be hyperpigmented or “salt and pepper” as in dark-skinned people. Rashes over the shoulders posteriorly and back in a “shawl” sign. It can be characteristic skin rash. The rash is often erythematous, peri-orbital, and purplish (heliotrepe) and may spread into the neck and back in a “shawl” sign, as in dark-skinned people. Rashes over the shoulders posteriorly and back in a “shawl” sign. It can be characteristic skin rash. The rash is often erythematous, peri-orbital, and purplish (heliotrepe) and may spread into the neck and back in a “shawl” sign.

**CONCLUSIONS**

The differential diagnosis of generalized weakness depends on the situation in which the patient is encountered. In general, patients seen after cardiothoracic procedures (especially extensive aortic repairs) tend to have ischemic myelopathies; patients in medical ICUs with critical illness, sepsis, or SIRS and on mechanical ventilation tend to have CIM, CIP, or prolonged NM blockade. Consideration of the common causes of neuromuscular weakness and adequate electrophysiological work-up will help to identify a large proportion of these patients with neuromuscular weakness. Nerve muscle biopsies play an important role in subclassification of the underlying syndrome and in prognosis. Although the predominant determinant of outcome is the underlying illness, supportive care is of paramount importance and a multidisciplinary approach to patient care is necessary to ensure a speedy and satisfactory functional recovery.

**REFERENCES**


Ventilation in the prone position in patients with acute lung injury/acute respiratory distress syndrome
Claude Guérin

Purpose of review
To contrast the beneficial effects of the prone position on the lungs and the lack of proven clinical benefits on patient outcome.

Recent findings
Recent human investigations in acute respiratory distress syndrome have shown that the prone position was able to abolish tidal expiratory flow limitation, to improve oxygenation in the case of localized infiltrates, to allow for reducing positive end-expiratory pressure level, and to reduce lung stress and strain. Experimental studies have confirmed that distribution of ventilation was more homogeneous in the prone position but showed that positive end-expiratory pressure affected ventilation distribution differently in the prone and in the supine position. Experimental work has also shown that proning reduced strains imposed on the lungs and made them more homogeneously distributed. Finally, one recent large randomized controlled trial of systematic proning in hypoxemic patients showed no reduction in mortality but less ventilator-associated pneumonia incidence in the prone position group.

Summary
The prone position is not systematically used in hypoxemic patients. Patients who could benefit from prone position sessions are those with the most severe acute respiratory distress syndrome and those with dorsal lung infiltrates. Whether this can be translated into improvement in patient outcome has yet to be tested in clinical trials.

Keywords
acute respiratory distress syndrome, prone position, respiratory mechanics

Abbreviations
ALI acute lung injury
ARDS acute respiratory distress syndrome
EELV end-expiratory lung volume
PEEP positive end-expiratory pressure
RCT randomized controlled trial
VALI ventilator-associated lung injury
VILI ventilator-induced lung injury
ZEEP zero end-expiratory pressure

Introduction
Ventilation in the prone position is an attractive means to improve oxygenation in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Growing experience with the prone position has largely confirmed that turning improves oxygenation in 70% of ARDS patients [1], sometimes dramatically [2]. The mechanisms of this technique are not completely understood in humans with ARDS. To date, however, preventing ventilator-associated lung injury (VALI) is as important as improving oxygenation for any ventilatory management. The evidence for the prone position preventing VALI is still limited in humans, whereas some animal studies suggest that the prone position may reduce ventilator-induced lung injury (VILI) [3]. Strictly speaking, VILI cannot be used in humans with ALI/ARDS just because injury from mechanical ventilation cannot be separated from underlying ALI/ARDS. In this situation the term VALI seems more appropriate. The term VILI was originally described in the experimental setting to point out that lungs injured by mechanical ventilation were healthy from the onset. An early multicenter randomized controlled trial (RCT) in ALI patients showed no effect on mortality [1] with the prone position compared with the supine position. This has been confirmed in a second large-scale trial [4]. Therefore, considering these negative results and some concerns about harmful effects, such as endotracheal tube kinking or displacement and pressure sores, there is some reluctance to routinely turn patients. The objective of the present review is to analyze original investigations released in the past 12 months about physiologic and clinical effects of the prone position during ALI/ARDS and to ascertain what we need to know and to do with this technique in the near future.
Effects of the prone position on respiratory mechanics in humans
Vieillard-Baron et al. [5**] demonstrated in 11 severely hypoxemic primary ARDS patients with intrinsic positive end-expiratory pressure and dynamic hyperinflation on zero PEEP (ZEEP) that the prone position reversed these abnormalities and improved gas exchange. These results suggested that the prone position abolished expiratory flow limitation and improved alveolar ventilation without increasing lung distension. The study of Vieillard-Baron et al. [5**] brings indirect evidence that, in humans with ARDS, the prone position can prevent repeated reopening and closure of small airways, and, hence, has the potential to abolish one of the components of VALI – low lung volume barotrauma [6]. In ARDS patients, the low functional residual capacity induces a reduction in the expiratory flow reserve promoting expiratory flow limitation, intrinsic PEEP and dynamic hyperinflation on ZEEP [7]. This phenomenon mainly occurs in the dependent dorsal areas of the lungs in the supine position. By increasing transpulmonary pressure in these areas, the prone position has two effects. The first is enhancement of the homogenization of distribution of tidal ventilation throughout the lungs, an effect which has been related to chest wall compliance reduction with the prone position [8]. The second is abolition of expiratory flow limitation, and, hence, reduction in intrinsic PEEP and dynamic hyperinflation. It should be noted that, in the study by Vieillard-Baron et al. [5**], a low level of external PEEP in the supine position, 6 cmH2O on average, set to counterbalance intrinsic PEEP on ZEEP, was also able to revert intrinsic PEEP and dynamic hyperinflation. Such low PEEP, however, could not improve alveolar ventilation.

Gainnier et al. [9] examined the effects of 0, 5, 10 and 15 cmH2O PEEP randomly assigned in both the supine and the prone position in 25 patients with primary ARDS and found that both interventions had an additive and not synergistic effect on oxygenation. In this study, however, and contrary to that of Vieillard-Baron et al. [5**], PaCO2 did not change with prone position. Differences in baseline PaCO2, ventilatory settings and distribution of infiltrates may account for this discrepancy. It is noteworthy that average intrinsic PEEP on ZEEP was twofold lower in the study of Gainnier et al. [9] than in that of Vieillard-Baron et al. [5**] (2 versus 4 cmH2O) for a greater respiratory rate (20 versus 15 breaths/ min) (Table 1). It should be noted that changes in PaCO2 during mechanical ventilation at a given minute ventilation can explain some changes in PaO2 for two reasons. First, concomitant reduction of PaCO2 and increase in PaO2 is likely to reflect improvement in alveolar ventilation, or more precisely an optimal match between alveolar ventilation and perfusion. The finding that PaO2 increases and PaCO2 does not simultaneously decrease should indicate that either cardiac output is lowered or alveolar dead space ventilation is increased by PEEP. The PEEP-induced increase in alveolar dead space may reflect lung overdistension. Second, Gattinoni et al. [10] found that the reduction in PaCO2 (PaCO2 responders) but not the increase in PaO2 (PaO2 responders) during the first prone

<table>
<thead>
<tr>
<th>Table 1 Respiratory mechanics in humans with primary acute respiratory distress syndrome during supine and prone position mechanical ventilation</th>
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<tbody>
<tr>
<td><strong>Vieillard-Baron [5</strong>]**</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Ventilatory settings</td>
</tr>
<tr>
<td>Tidal volume (ml/kg)</td>
</tr>
<tr>
<td>Respiratory rate (breaths/ min)</td>
</tr>
<tr>
<td>Respirator</td>
</tr>
<tr>
<td>Respiratory mechanics on ZEEP in the supine position</td>
</tr>
<tr>
<td>Intrinsic PEEP (cmH2O)</td>
</tr>
<tr>
<td>Plateau pressure (cmH2O)</td>
</tr>
<tr>
<td>Pflex (cmH2O)</td>
</tr>
<tr>
<td>Quasi-static compliance (ml/cmH2O)</td>
</tr>
<tr>
<td>Linear compliance (ml/cmH2O)</td>
</tr>
<tr>
<td>Effects of the prone position on ZEEP</td>
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<tr>
<td>Intrinsic PEEP</td>
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<tr>
<td>Plateau pressure</td>
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<td>Quasi-static compliance</td>
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<td>Linear compliance</td>
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<tr>
<td>Effects of PEEP in the supine position</td>
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<td>Intrinsic PEEP</td>
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<td>Plateau pressure</td>
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<td>Pflex</td>
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<tr>
<td>Quasi-static compliance</td>
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<tr>
<td>Linear compliance</td>
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</table>

m, measured body weight; p, predicted body weight; ZEEP, zero end-expiratory pressure; PEEP, positive end-expiratory pressure; Pflex, point at which marked increase in compliance can be observed.
position session predicted improved patient outcome. Therefore, given that in the study of Ganniers et al. [9] PaCO₂ did not decrease with prone position and PEEP and that prone position and PEEP had additive effects on oxygenation, this means that PEEP has to be reduced in the prone position. In the study of Gannier et al. [9] the prone position, but not PEEP, improved oxygenation in patients with localized infiltrates, a situation in which PEEP in the supine position is likely to promote lung overdistension [11–13].

Taken together, the results from Vieillard-Baron et al. [5**] and Gannier et al. [9] suggest that the prone position should be used in severe hypoxemic ARDS patients, with localized infiltrates and associated with a level of PEEP either low or lowered relative to the supine position.

**Effects of prone position on distribution of lung perfusion and ventilation**

Earlier experimental studies found that even though lung perfusion was slightly redistributed to the most anterior parts of the lungs in the prone position, it remained prevalent in lung dorsal areas. An opposite finding, however, was expected according to the law of gravity. So, the distribution of perfusion within the lungs is not primarily driven by the effect of gravity and remains prevalent in dorsal regions whatever the position.

The regional distribution of ventilation during mechanical ventilation has recently been investigated using high-resolution techniques [14*]. The results of this study have largely confirmed previous data and analyzing them summarizes the body of knowledge on ventilation distribution. Anesthetized and mechanically ventilated normal sheep were studied on ZEEP and PEEP 10 in the supine and prone position [14*]. In the supine position on ZEEP the vertical ventral to dorsal distribution of ventilation was not linear but unimodal with the mode of ventilation at the central lung region. With PEEP 10 the mode was shifted towards the dorsal regions. In the prone position on ZEEP the ventilation linearly increased from dorsal (nondependent) to ventral (dependent) regions. It was computed that ventilation was greater by 3.2 fold in the ventral than in the dorsal regions. With PEEP the linear relationship between lung ventilation and vertical height disappeared. The isogravitational heterogeneity of ventilation was reduced by PEEP in the supine and prone position. The gravitational component of ventilation heterogeneity was increased in the supine and decreased in the prone position with PEEP. The heterogeneity of ventilation was less in the prone than in the supine position and was minimal with PEEP in the prone position. PEEP redistributed ventilation towards dependent regions in the supine position and towards non-dependent regions in prone position.

**Effects of the prone position on ventilator-induced lung injury**

Mentzelopoulos et al. [15**] investigated 10 patients with severe ARDS (Pao₂/Fio₂ < 100 under Fio₂ of 0.79 ± 0.07). PEEP (9.4 ± 1.3 cmH₂O) and tidal volume (Vt) (9.0 ± 0.9 ml/kg predicted body weight) were set to maintain lung plateau pressure below 30 cmH₂O. Patients were studied in a 60° semi-recumbent position, then in the prone position and again in 60° semi-recumbency. End-expiratory lung volume (EELV) during mechanical ventilation was measured using the helium dilution technique. The interest of this study is that overall parenchymal lung stress and lung strain, the two components of VALI, were assessed from transpulmonary plateau pressure and tidal volume/EELV ratio, respectively. The authors found that both indexes were reduced with the prone position relative to semi-recumbency. This is the first study showing that in humans the probability of VALI can be reduced by the prone position.

The study by Mentzelopoulos et al. [15**] approached VALI indirectly and globally. In normal rats, Valenza et al. [16**] provided more direct and regional information on VILI. They showed that the prone position delayed occurrence of VILI compared with the supine position, from 73 to 112 min after onset of mechanical ventilation using tidal volume of 34 ml/kg, that is 90% of the total lung capacity. The prone position was associated with a more homogeneous distribution of lung strains assessed from computed tomography (CT) scan. This study suggests that the changes in distribution of alveolar ventilation with the prone position may explain the observed distribution of lung strains.

**How to optimize practical application of the prone position in humans**

Reignier et al. [17] found that enteral nutrition was poorly tolerated in the prone position, with more vomiting episodes and greater residual gastric volumes than in the supine position. Enteral nutrition practice should be optimized if delivered in the prone position by using prokinetic agents, transpyloric feeding and semi-recumbency. It should be noted that in one RCT detailed below [4*], the incidence of ventilator-associated pneumonia was reduced in the prone position group.

Bein et al. [18] found that complete prone position (180°) for 6 h led to better oxygenation, higher compliance and less side effects than the incomplete (135°) prone position.

**Effects of the prone position on patient outcome**

Guéria et al. [4*] completed a large multicenter randomized controlled study in France to test the hypothesis
Table 2 Summary of the three multicenter prospective randomized controlled trials of prone position in acute lung injury/acute respiratory distress syndrome

<table>
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<tr>
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<tbody>
<tr>
<td>No. patients analyzed</td>
<td>152</td>
<td>378</td>
<td>60</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Acute lung injury (PaO2/FIO2 &lt; 300)</td>
<td>PaO2/FIO2 &lt; 300</td>
<td>ARDS (PaO2/FIO2 &lt; 200)</td>
</tr>
<tr>
<td>Dose of PP per day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planned</td>
<td>At least 6 h</td>
<td>At least 8 h</td>
<td>20 h</td>
</tr>
<tr>
<td>Randomization</td>
<td>7 h</td>
<td>8 h</td>
<td>13 h</td>
</tr>
<tr>
<td>Tidal volume (ml/kg)</td>
<td>10.3 ± 2.9 p</td>
<td>8.1 ± 1.9 m</td>
<td>8.6 ± 1.5 i</td>
</tr>
<tr>
<td>PEEP (cmH2O)</td>
<td>9.6 ± 3.2</td>
<td>7.5 ± 3.2</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>FIO2 (%)</td>
<td>72.7 ± 18.7</td>
<td>66.7 ± 20.4</td>
<td>79 ± 21</td>
</tr>
<tr>
<td>PaO2/FIO2</td>
<td>129.5 ± 48.5</td>
<td>155 ± 59</td>
<td>159 ± 22*</td>
</tr>
<tr>
<td>PaCO2</td>
<td>44.2 ± 11.8</td>
<td>44 ± 11</td>
<td>43 ± 11</td>
</tr>
<tr>
<td>pH</td>
<td>Not provided</td>
<td>7.39 ± 0.10</td>
<td>45 ± 9</td>
</tr>
<tr>
<td>Mortality</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>Unchanged</td>
</tr>
<tr>
<td>VAP incidence</td>
<td>Not assessed</td>
<td>Significantly reduced in PP group</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>Improved in PP group</td>
<td>Improved in PP group</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Duration of MV</td>
<td>Unchanged</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>More pressure sores in PP group</td>
<td>Pressure sores, endotracheal tube obstruction or displacement more frequent in PP group</td>
<td></td>
</tr>
</tbody>
</table>

To date, the three RCTs completed in hypoxemic patients (Table 2) led to negative results. Limitations that explain these negative results are lack of power, insufficient dose of the prone position, mechanical ventilation not used according to current recommendations, and heterogeneous patients. Positive results favoring the prone position were, however, obtained from a post-hoc analysis. In the Italian trial [1], 10-day mortality was significantly less with the prone position in the most severely hypoxemic patients (PaO2/FIO2 < 88 quartile at randomization) and also in those with the highest general severity score and the greatest tidal volume (> 12 ml/kg quartile). In the multivariate analysis of the Spanish trial [19], the prone position was an independent risk factor associated with increased patient survival.

Conclusion

During the last 15 years numerous studies consistently described the beneficial effects of the prone position on the lungs. Originating with marked improvement in oxygenation it has now become clear that the prone position can distribute ventilation, VILI and lung strains more homogeneously throughout the lungs. The mechanisms for this are not fully understood and include gravity, lung structure and other unknown factors. Therefore, the prone position can improve oxygenation without inducing and even by preventing lung overdistension/hyperinflation. Hence, the prone position is a full component of a lung protective ventilatory strategy and a smart way to manage severe ARDS patients. The question is whether the prone position can be strongly recommended because a high level of clinical evidence is
lacking. Since patient outcome in ARDS regularly improves with the improvement in patient care and mechanical ventilation, it is now difficult for an intervention to prove its efficiency. Alternatively, even though turning prone is apparently simple with a low economical burden, its practice in daily intensive care unit life is still associated with some side effects, the incidence of which should be reduced by implementation of guidelines. Another RCT in the most severe ARDS patients, completed up to the required power, is mandatory, therefore, to clarify the impact of the prone position on outcome.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 67).

Meta-analysis of controlled trials of ventilator therapy in acute lung injury and acute respiratory distress syndrome: an alternative perspective

John L. Moran  
Andrew D. Bersten  
Patricia J. Solomon

Abstract  Objective: The role of protective ventilation in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) is controversial. Evidence was sought from published randomised trials for a consistent treatment effect of protective ventilation and any covariate modification. Design: Meta-analysis of protective ventilation trials in ALI/ARDS and meta-regression of covariates on treatment effect (log odds ratio), with respect to 28-day mortality. Heterogeneity impact on the meta-analysis was assessed by the $H$ statistic (substantial impact, >1.5) and graphical analysis. Five trials with a total of 1,202 patients were considered. Measurements and results: Average 28-day mortality was 0.40 in the treatment group (protective ventilation, $n=605$) vs. 0.46 in the control group (control ventilation, $n=597$). The treatment effect (odds ratio) was: fixed-effects, 0.71 (95% CI 0.56–0.91, $p=0.006$; heterogeneity, $p=0.06$) and random effects: 0.80 (95% CI 0.49–1.31, $p=0.37$). Heterogeneity impact ($H$ statistic=1.50) was adjudged as modest. The treatment effect was significant and (a) favoured protective ventilation for a tidal volume less than 7.7 ml/kg predicted (treatment group) and a mean plateau pressure of 30 cmH$_2$O or higher (control group) but was not influenced by plateau pressure 21–30 cmH$_2$O (treatment group) and (b) depended upon plateau pressure difference greater than 5–7 cmH$_2$O between protective ventilation and standard ventilation. Conclusions: Overall treatment effect estimate favoured protective ventilation but did not achieve statistical significance. Protective ventilation depended upon threshold levels of tidal volume, plateau pressure, and plateau pressure difference.

Keywords  Meta-analysis · Acute lung injury · Acute respiratory distress syndrome · Heterogeneity · Meta-regression · Plateau pressure

Introduction

The recently reported trial of “low” (6 ml/kg predicted body weight) tidal volume ventilation in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) by the ARDS Network [1] in 2000 appears to have established the efficacy of this ventilatory strategy although initial concerns were expressed in correspondence regarding the “unconventionally high plateau pressures in the group treated with traditional tidal volumes” [2]. The smaller difference in plateau pressures between treatment arms had already been advanced in the accompanying editorial [3] to the ARDS Network publication as a potential reason for the failure to demonstrate a treatment effect in three previous trials [4, 5, 6] of lung protective ventilation. Similarly, an editorial in early 2002 reviewing what was “best for ARDS management” concluded that, “These studies do not tell us whether ARDS patients should be ventilated with a tidal volume of 6 ml/kg body weight or simply only less than 12 ml/kg” [7].
Against this background, two more recent papers have added to the debate on protective ventilation; a meta-analysis [8] of the five randomised controlled trials of this intervention [1, 4, 5, 6, 9] and a health policy report detailing the institutional responses to the controversies over “How best to ventilate” [10]. Considerable retort has followed this meta-analysis: an editorial [11], correspondence from the original ARDS Network [12] trial authors and exchanges over the detail of both the meta-analysis and the trials.

The purpose of the present analysis is to contribute to the “continued scrutiny” [13] of the trials above, an endeavour parallel to that of the recent review by Petrucci and Iacovelli [14]. First, we departed from the approach of Eichacker et al. [8] who grouped the trials into beneficial/non-beneficial based upon heterogeneity and thus did not consider the implications of a pooled estimate of the efficacy of protective ventilation. Second, and contingent upon this pooled estimate, we investigated the underlying cause(s) of the heterogeneity using meta-regression [15]. Rather than the existence of heterogeneity precluding the finding of covariate modification of the pooled estimate [16, 17], the “primary value of meta-analysis is in the search for predictors of between-study heterogeneity” [18] and serves also to formalise the attempt by Eichacker et al. [8] to relate plateau pressure and mortality. Devoid of a pooled estimate, there is limited ability to examine those variables which may have determined heterogeneity [11]. Third, we highlight the question of the cause of the observed treatment effect in the two “positive” trials [1, 9]: an increase in control mortality as a consequence of high plateau pressures or decrease in treatment arm mortality due to low plateau pressures.

Some debate has occurred over the propriety of the increment of mechanical tidal volume in the treatment arm of the ARDS Network trial [19]; this question is not directly canvassed; rather the comment by Senn [20] is noted: “Clinical trials are not and never will be representative of general medical practice”.

## Methods

The study population comprised the five trials [1, 4, 5, 6, 9] identified above [8] using protective ventilation in ALI/ARDS. The outcome end-point was 28-day mortality except for the Brower et al. [5] and Stewart et al. trials [6], where hospital mortality was used. Data for 28-day outcomes in both the Multicenter Trial group on Tidal Volume Reduction in ARDS (trial report, 60 day outcome [4]) and the ARDS Network Trial (trial report, 180 day outcome [1]) were supplied on request to the study authors. The relationship between Acute Physiology and Chronic Health Evaluation (APACHE) versions III and II scores was deemed to be: APACHE III score=4.48+3.259 /C148APACHE II score (\(R^2=0.81, P=0.0001\)). This was based upon a sample of 73,000 patients from the Aus-

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<td>37.3</td>
<td>30.6&lt;sup&gt;b&lt;/sup&gt;</td>
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<sup>a</sup> Hospital mortality
<sup>b</sup> Days 1–5
<sup>c</sup> Averaged over first 7 days
Results

The meta-analytic fixed effect pooled estimate (OR) of treatment effect (protective vs. control ventilation) was 0.71 (95% CI 0.56–0.91, p=0.006). However, heterogeneity was present at a p value of 0.06 (as assessed by the Q and Breslow-Day test and at 0.08 by the Zelen exact test). The H and I² statistics were 1.5 and 56.8%, respectively. The corresponding random effects estimate was 0.80 (95% CI 0.49–1.31, p=0.37). A “Forrest plot” of the random effects estimates is presented in Fig. 1, with trial weights reflected as the point-estimate box size; the non-significant pooled estimate favoured protective ventilation. The Galbraith plot (Fig. 2) revealed substantial horizontal displacement of the ARDS Network trial due to its size and some scatter of the other trials between the confidence intervals, but, importantly, no trial was outside this range. Similarly, the influence analysis failed to show a substantive effect of deletion of any one trial on the “deleted” estimate with respect to the overall point esti-
The implication of these two graphical displays was that heterogeneity was, at worst, modest, in agreement with the value of the $H$ and $I^2$ statistics. This impression was supported by the cumulative meta-analysis, which demonstrated an initial shift of the point-estimates over time, but these estimates became relatively stable at approx. OR=0.8 with the last three trials [1, 4, 6] and 95% confidence intervals of treatment effect spanned OR=1 from the second trial (Brower et al. [5]) onwards (Electronic Supplementary Material, Fig. E2.2).

The meta-regression of mechanical tidal volume vs. log OR yielded a significant relationship for the treatment ventilation arm ($p=0.05$) such that below a tidal volume of 7.7 ml/kg-predicted the log OR fell below 0 (≥ OR of 1) and a benefit, treatment vs. control was evident (Fig. 3, left panel). A borderline significant relationship for the control ventilation arm ($p=0.08$) was also evident such that above a tidal volume of 11.2 ml/kg-predicted the log OR fell below 0 (≥ OR of 1) and a detriment, control vs. treatment, existed. The log OR also showed a significant relationship ($p=0.004$) with tidal volume difference (control vs. protective ventilation) such that log OR was less than 0 (OR <1) for a tidal volume difference greater than 4.2 ml/kg-predicted (Electronic Supplementary Material, Fig. E2.3).

Between plateau pressure and log OR on day 1 a significant relationship was demonstrated for the control ($p=0.02$) but not treatment ($p=0.18$) ventilation arm (Fig. 4) such that beyond a control plateau pressure of 29–30 cmH$_2$O the log OR fell below 0 (≥ OR of 1) and a benefit, treatment vs. control, existed. Seen somewhat differently (Fig. 5, left panel), a plateau pressure difference (control vs. protective ventilation, day 1) greater than 5.5 cmH$_2$O was associated with treatment arm benefit. Over days 1–7 a similar relationship between plateau pressure difference and log OR was seen, but the benefit for the treatment arm required a plateau pressure difference greater than 7 cmH$_2$O (Fig. 5, right panel).

The univariate relationship between log OR and VPP (average plateau pressure over days1–7) was significant for control ventilation (VPP 310–530 ml/kg-predicted per 1 cmH$_2$O) such that for a VPP greater than 355 ml/kg-predicted per 1 cmH$_2$O the log OR was less than 0 and a benefit, treatment vs. control, existed ($p=0.004$; Electronic Supplementary Material, Fig. E2.4, right panel). For protective ventilation (VPP 160–200 ml/kg-predicted per 1 cmH$_2$O) no relationship with OR was demonstrated ($p=0.26$; Electronic Supplementary Material, Fig. E2.4, left panel).

No multivariable regression was significant ($P$ always >0.12 for individual regression coefficients) and no simple quadratic (non-linear effect) of volume, plateau pressure or VPP was demonstrated.

**Discussion**

Combining or splitting

The original meta-analysis [8] based its strategy of separate consideration of beneficial ($n=2$)/non-beneficial trials ($n=3$) upon the non-homogeneity of odds ratio as diagnosed by the Breslow-Day test ($p=0.06$). Using data from this meta-analysis [8] the pooled fixed effects estimate of treatment effect was calculated as 0.76 (95% CI 0.60–0.95, $p=0.02$), with heterogeneity being present at $p=0.064$ (Q and Zelen exact tests). The corresponding
random effects estimate was 0.83 (0.52–1.34, \( p = 0.43 \)).

For the current meta-analysis, which incorporated 28-day survival estimates for two trials [1, 4], not given in the initial trial reports, heterogeneity was also diagnosed at similar \(( p)\) levels. There was also evidence of clinical heterogeneity between the trials in terms of ventilation (the levels of positive end-expiratory pressure employed) and patient type (enrolment of those at risk of ARDS and number of organ failures). However, the heterogeneity was assessed as being of modest impact upon the (pooled) results of the current meta-analysis \((H\) and \(I^2\) statistics), this supposition also being reflected in the graphical analyses. Thus the heterogeneity did not preclude the consideration of a consistent random effects pooled estimate [27], which was non-significant \(( p>0.05)\).

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**Trial conduct**

As noted [12], four of the trials were stopped early because of efficacy [1, 9] or futility [4, 5], and such premature termination is known to bias treatment effects in individual trials [28]. Exaggeration of treatment effects also occurs when interventions are conducted in a non-blinded manner [29], as was obviously the case in the trial ventilation protocols. More importantly, the use of “stopping rules” may induce artificial heterogeneity into overviews of clinical trials [30] and increase the type I error rate in tests of homogeneity [31]. Heterogeneity may be assessed in trials where early stopping did not occur in order to quantify the impact of early stopping upon heterogeneity [30], but such an estimate is obviously vitiated in the current meta-analysis by the small number of such trials (one; [6]). However, it may be surmised that the heterogeneity detected in both the current and original meta-analysis was incremented by early stopping.
Heterogeneity predictors

Within the range of mechanical tidal volumes used in protective ventilation in the five trials a beneficial trial effect, at \( p = 0.05 \), was demonstrated (log OR<0) with tidal volumes less than 7.7 ml/kg-predicted in the treatment arm, whereas adverse effects were noted with control tidal volumes greater than 11.2 ml/kg-predicted, albeit at \( p = 0.08 \) (Fig. 3). Adverse effects (Fig. 4) of plateau pressure appeared at values higher than 30 cmH\(_2\)O (achieved in the control group only), a threshold similar to that identified by Petrucci and Iacovelli [14], although the latter used subset analysis at an empirical threshold rather than derivation from a general (meta-)regression approach. Thus our results counter the claim that “as long as tidal volumes produce airway pressures between 28 and 32 cmH\(_2\)O, there is no benefit from using low tidal volumes... and it may be harmful” [8] and support the conclusions (based upon an individual patient analysis) of Amato et al. [32], who noted “no evidence of harm of the lower tidal volume strategies”. However, their analysis was restricted to the three “non-beneficial trials” [4, 5, 6], and their use of non-linear (Cox) regression models to analyse and (covariate) adjust the results is known to increase the variance of treatment estimates (and displace them from the null [33]), as illustrated by the 95% CI of the “best adjusted” model compared with the “univariate” model (Fig. 1 in [32]). The claim in reply by Eichacker et al. [34] that, “Even the ‘best adjusted’ 95% confidence intervals suggest that there is a one in three chance that low tidal volumes produce an increase in mortality rates” must be understood in this context. Moreover, the interpretation given to these (95%) confidence intervals is somewhat problematic: the apposite interpretation of a 95% CI of a parameter \( \theta \) is that in (an infinite number of) repetitions of a study, an exact proportion (95%) of all such intervals would enclose \( \theta \). Once the data have been collected, and a single 95% CI has been calculated, the probability that \( \theta \) lies within this CI is now 0 or 1, that is,
A log OR–VPP relationship was established for VPP greater than 355 ml/kg-predicted per 1 cmH₂O, which levels were seen only with control ventilation; no relationship was evident for the VPP range of protective ventilation. However, caution needs to be exercised over the interpretation of VPP [35], as it represents an interaction term and the “main effects”, volume and plateau pressure, were not significant in a multivariable meta-regression (see above).

The treatment effect favouring protective ventilation was also dependent upon the existence of a threshold difference (control vs. treatment ventilation) of both tidal volume and plateau pressure. Thus “modest” increases in mean plateau pressure from 30 to 33 cmH₂O after randomisation in the control group of the ARDS Network trial [36] may not have been benign. The results of a further ARDS Network subanalysis suggesting that “intermediate tidal volumes and inspiratory pressures are not as safe as the lower tidal volumes and pressures used in...” [36] have not been confirmed by the current meta-analysis and appear to need formal trial demonstration. Although disagreeing in principle with the editorial response [11] to the Eichacker et al. [8] meta-analysis over the question of the integrity of the pooled effect estimate, the above results are supportive of the conclusion in the editorial that “high plateau pressures in the control arms likely contributed to the observed differences in mortality”.

Critique of methodology

The small number of trials considered in both the meta-analysis and the meta-regression and the consequent inability to effectively test for multivariate regression and non-linear relationships [37] are problematic. The varying methods of prescribing ventilator tidal volume (four different prescription units [12]) and measuring plateau pressure [11] may have led to a considerable degree of uncertainty in the summary estimates of both tidal volume...
and plateau pressure and in the statistical relationships described between these two variables and the treatment effect, as log OR (in particular the significance levels achieved relative to \( p=0.05 \)). Furthermore, the relationships discerned may be associations across trials and have neither a causal interpretation nor reflect within-trial relationships [15]. This being said, the overall quantitative threshold findings of tidal volume and plateau pressures are consistent with clinical and experimental evidence [7].

Conclusions

The pooled estimate of treatment effect of in ALI/ARDS favours protective ventilation, but it failed to achieve statistical significance on random effects estimation. Early stopping in four of the five trials considered may have been a factor contributing to heterogeneity. In ALI and ARDS mechanical ventilation with low tidal volumes is not detrimental and may have advantage below threshold levels of 7.7 ml/kg-predicted. Further trials, with standardised prescription of ventilatory parameters, appear to be necessary to define optimal mechanical ventilation in ALI/ARDS.

Reference

Introduction

Once upon a time the existence of ventilator-induced lung injury (VILI) was debated. After all, most patients with lung dysfunction requiring mechanical ventilation had other potential causes of lung injury, and many patients appeared to tolerate mechanical ventilation for prolonged periods without any adverse sequelae. However, as a result of numerous studies over the past century, and especially during the past 20 years it is now generally accepted that mechanical ventilation per se can initiate as well as exacerbate lung injury and contribute to patient morbidity and mortality. This review examines the seminal bench and bedside studies that contributed to our current understanding of VILI, and that form the basis for current recommendations for mechanical ventilation of the critically ill. Figure 1 schematically depicts a timeline of bench to bedside research on VILI. Included in this review are many of the most frequently cited studies (with the number of citations, N, from the Institute for Science Information Citation Index as of August 2005 included in parentheses), as well as those studies which the authors feel have had a particularly significant impact on subsequent research and/or clinical practice.

Brief overview of the early years: air leaks, surfactant dysfunction, and “respirator lung”

As early as the 1700s investigators raised concerns that inflation of the lung with positive pressure ventilation could potentially damage the lungs and produce air leaks (for an excellent historical review see [1]). In 1887 Champneys [2] reported that lung rupture and cervical emphysema ensue if the lungs of dead infants are subjected to pressures of 20–80 mmHg. In 1939 Macklin [3] published a frequently cited study demonstrating that excessive alveolar distension produces rupture at the junction of the alveolar wall and vascular sheath, allowing air to track along the bronchovascular sheath into the mediastinum and subcutaneous tissues or to rupture into the pleural or peritoneal spaces. Given that the development of air leaks appeared to be related to the use of high airway pressures, the term “barotrauma” was applied.

In addition to air leaks, laboratory investigations also demonstrated that mechanical ventilation can adversely affect lung compliance and surfactant function. Greenfield et al. [4] (N=115) showed that ventilation of dog lungs with large tidal volume (Vt; generated with a peak inspiratory pressure, PIP, of 36–32 cmH2O) for 2 h produces surfactant dysfunction, and Faridy et al. [5] (N=178) observed in an ex vivo dog lung model that the addition of positive end expiratory pressure (PEEP) attenuates ventilation-induced increases in surface tension.

Early investigators also made a number of important observations. For example, in 1949 Fowler [6] (N=325)
published a key observation that would be revisited in later studies of VILI: the fact that ventilation in lungs is not uniform, particularly in the presence of underlying lung disease. Mead et al. [7] (N=584) published an often cited paper examining the forces acting on alveoli within the lung. They illustrated that although uniform force proportional to the transalveolar pressure acts on adjacent alveoli in a uniformly expanded lung, the traction forces exerted by adjacent expanded alveoli on the walls of a collapsed alveolus can greatly exceed transpulmonary pressure (e.g., exceed 140 cmH₂O) due to interdependence.

On the clinical front, the use of mechanical ventilation as a supportive therapy outside the operating theater became increasingly widespread in the aftermath of the polio epidemics of the 1950s, and the term “respirator lung” started being applied to autopsy findings of diffuse alveolar damage (dense pulmonary cellular infiltrates, pulmonary edema, and hyaline membranes) in critically ill patients who had required ventilation with high airway pressures prior to death. Indeed, when Ashbaugh et al. [8] (N=1193) submitted their landmark paper in 1967 on acute respiratory distress (ARDS) in adults, one reviewer purportedly dismissed this “new” syndrome as simply a manifestation of VILI [9].

Recognizing that it would be impossible in the clinical arena to dissect out the contribution of ventilator-induced injury from lung injury due to other causes, investigators turned to the bench.

**Seminal bench studies on ventilator-induced injury**

The initial challenge tackled by investigators was determining whether mechanical ventilation per se could produce diffuse lung injury (i.e., “respirator lung”), and if so, what ventilatory parameters (e.g., VT, end-expiratory pressure) were responsible.

Can mechanical ventilation produce lung injury other than air leaks, and at what ventilatory settings?

A landmark paper examining this question was published by Webb and Tierney [10] (N=374) in 1974 entitled “Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure.” Realizing that “some patients with ARDS may require pressures of 40–80 cmH₂O,” Webb and Tierney set out to determine whether the “only complications of these pressures involve lung rupture with interstitial emphysema or pneumothorax.” Their study design consisted of ventilating rats with normal lungs with PIP values of 14, 30, or 45 cmH₂O without PEEP, as well as with PIP of 30 or 45 cmH₂O and 10 cmH₂O of PEEP. In order to maintain similar PaCO₂ with the various ventilation strategies the dead space of the ventilatory circuit was altered.

This seminal study had several key findings. First, in keeping with prior studies, Webb and Tierney demonstrated that ventilation of normal lungs with low pressures...
(PIP 14 cmH₂O) does not cause significant injury. Second, they dramatically showed that ventilation with high pressures (30 or 45 cmH₂O) produces perivascular edema, and that ventilation at high airway pressures (45 cmH₂O) without PEEP leads to severe lung injury (gross pulmonary edema, severe hypoxia) as well as death within 35 min. Third, they showed that PEEP confers protection from alveolar edema due to high inspiratory pressure ventilation.

Based on the results of this study, Webb and Tierney set forth a number of precepts that future research would validate: (a) that lungs from patients with ARDS have some “normal alveoli scattered among collapsed or fluid-filled alveoli, and that although the flooded alveoli “may be protected from over inflation... we are concerned that the normal alveoli may be over inflated and damaged,” (b) that “tissue disruption secondary to a high inspiratory pressure is probably not the mechanism of the changes we observed,” and (c) that surfactant dysfunction with certain ventilatory strategies likely contributed to the development of lung injury. Prophetically, they concluded with the comment that the results “have influenced our management of patients requiring ventilatory assistance. We avoid the use of high inspiratory pressure positive pressure breathing, especially if the end-expiratory volume is low, as for example in patients with ARDS...” and “in such situations we strive to avoid high inspiratory pressures, use a low frequency, and apply PEEP” (quite similar to current recommendations decades later).

However, the study by Webb and Tierney (and other animal studies to follow) had a number of significant limitations. As would subsequently become even more apparent, different species have different susceptibility to VILI (i.e., small species are generally more susceptible). Therefore it remained uncertain whether the bench findings were applicable to humans. Second, the period of ventilation in this study was only approx. 60 min (N.B. short periods of ventilation are a limitation of most bench studies). As such, it remained unclear whether the results were applicable to the lung injury found with longer periods of ventilation. Third, hemodynamic parameters were not measured or controlled between groups and lung volumes (e.g., VT, end-inspiratory volume) were not measured. Thus it remained unclear whether other factors (e.g., hypotensive shock) may have contributed to the lung injury. Finally, the study did not dissect out the mechanisms responsible for high inspiratory pressure VILI.

What ventilatory parameters are injurious and how?

In a series of eloquently designed experiments Dreyfuss and colleagues [11, 12, 13] explored which of the many parameters of mechanical ventilation (e.g., VT, PIP, end expiratory lung volume) is responsible for the development of pulmonary edema, and whether the physiological changes seen with injurious ventilation are associated with any ultrastructural changes (as assessed by electron microscopy). In their 1985 paper Dreyfuss et al. [11] demonstrated that high pressure (PIP 45 cmH₂O) ventilation of rat lungs in vivo increases extravascular water and lung albumin uptake rapidly (within 5 min of ventilation), and that with longer periods of ventilation (up to 20 min) a progressive increase in lung injury occurs (i.e., endothelial cell detachment and blebs progressing to diffuse injury including denudation of the epithelial basement membrane, interstitial and alveolar edema with hyaline membranes and cell debris) [11] (N=364). This study illustrated that injurious ventilation of normal lungs could not only produce ultrastructural cellular damage, but that this injury occurs within minutes of initiating an injurious ventilation strategy.

Dreyfuss et al. [12] (N=503) also explored whether it was the high airway pressure per se or the resulting lung volume that leads to VILI and pulmonary edema. In order to differentiate the effect of airway pressure from that of lung volume rats were subjected to one of the following five ventilatory strategies: (a) low PIP (7 cmH₂O) resulting in relatively low VT (13 ml/kg); (b) high PIP (45 cmH₂O) resulting in high VT (40 ml/kg); (c) high PIP (45 cmH₂O) and 10 cmH₂O PEEP (VT 25 ml/kg); (d) high PIP (45 cmH₂O) but restricted VT (19 ml/kg, produced by using a thoracoabdominal binder to limit chest wall excursion); and (e) negative inspiratory pressure (using a mini-iron lung) and high VT (44 ml/kg). The key finding of this study was that high VT ventilation, irrespective of airway pressure, produces severe lung injury characterized by pulmonary edema, increased alveolar-capillary permeability, and structural abnormalities. In contrast, ventilation with lower VT, irrespective of airway pressure, does not produce ultrastructural changes or signs of alveolar edema or hemorrhage. In addition, PEEP once again was found to be “protective,” as the presence of PEEP prevented pulmonary epithelial damage and alveolar edema and significantly reduced interstitial edema and endothelial cell changes. As a result of this study (and several confirmatory studies in other models, see [13]), researchers began to focus on “volutrauma” (i.e., injury due to lung volume which is proportional to the transmural pressure gradient across the alveolus) rather than “barotrauma” (injury due to airway pressure) as the predominant injurious ventilatory parameter. These results agreed with Bouhuys’ [14] observation in Nature in 1969 that musicians playing the trumpet repetitively develop pressures at the airway opening of approx. 150 cmH₂O without developing lung injury. Further laboratory studies showed that ventilation with either high VT or high end-inspiratory lung volume is detrimental [13].

Meanwhile, other investigators such as West et al. [15] and Parker et al. [16, 17] focused on the injurious forces acting on the opposite side of the thin (<0.4 μm) alveolar...
capillary interface, i.e., the endothelial surface. Using isolated perfused rabbit lungs, West et al. [15] (N=230) examined the role of three of the major forces acting on the pulmonary capillary wall (circumferential tension due to transmural pressure, surface tension of the alveolus, and longitudinal tension due to lung inflation) and demonstrated that at high lung volume or with high perfusion pressure, capillary stress failure greatly increases.

Multiple investigators also explored the relationship between PEEP and VILI (including what level of PEEP is associated with reduced alveolar edema, surfactant dysfunction, histological injury, and improved gas exchange). Studies showed that in experimental models in which excessive lung distension could occur with high PEEP (e.g., open chest models or ex vivo lungs), high PEEP worsened lung edema. However, with in vivo models in which lung volume was restricted by the chest wall, high PEEP resulted in cardiovascular compromise and was associated with either increased or decreased pulmonary edema. The particular level of PEEP that was injurious appeared to depend on a number of factors including the experimental model, animal species, and end-inspiratory lung volume (with similar PEEP leading to more adverse sequelae in ex vivo models, smaller species or with large lung volumes) [13].

Conversely, ventilation without PEEP did not appear to cause significant injury, provided low airway pressure/physiological V\textsubscript{i} was used in normal lungs in vivo (i.e., with intact negative pleural pressure to maintain end-expiratory lung volume) for short periods of time. However, ventilation with low PEEP or no PEEP in ex vivo lungs, or lungs with surfactant dysfunction (such as occurs with high V\textsubscript{i} ventilation) was associated with lung injury and dysfunction. For example, in an ex vivo rat lung model Muscedere et al. [18] (N=332) illustrated that ventilation using PEEP below the inflection point of the pressure-volume curve resulted in significant distal airway injury and reduced lung compliance as compared to the minimal injury found if PEEP greater than the inflection point was used. These studies led to a new concept in VILI—“atelectrauma” (injury from repetitive opening and collapse of distal lung units due to insufficient end-expiratory lung volume) [19] (N=46).

Factors that predispose to ventilator-induced lung injury

Multiple bench studies have also identified a number of factors (such as underlying lung disease, systemic inflammation, surfactant dysfunction, aspiration, pulmonary edema, extremes of age, heterogeneous lung ventilation) that increase the susceptibility of lungs to injury by mechanical ventilation. Often a synergistic interaction was found between mechanical ventilation and a preexisting lung abnormality. For example, in isolated perfused rabbit lungs Hernandez et al. [20] (N=63) demonstrated that, individually, oleic acid or ventilation with PIP of 25 cmH\textsubscript{2}O has negligible effects on lung capillary filtration coefficients. However, when the insults are combined, severe lung injury (pulmonary edema, hyaline membranes, and extensive alveolar hemorrhage) ensue. Similarly, they found that age or surfactant inactivation predisposes to increased injury with subsequent mechanical ventilation [21, 22], and Dreyfuss et al. [23] (N=93) demonstrated a synergistic interaction between high volume ventilation (V\textsubscript{i} 45 ml/kg) and pretreatment of rats with α-naphthylthiourea (a drug that increases alveolar capillary permeability and edema). Of the various factors studied particular attention was paid to surfactant dysfunction, given its prevalence in both neonatal respiratory distress and in adult lung disorders such as aspiration and lung sepsis (for review see [24]).

Several explanations have been put forth as to why such preexisting lung abnormalities increase the susceptibility to mechanical VILI. First, for structural disruption to occur the magnitude of force applied must exceed the resilience of the underlying lung parenchyma. Thus it follows that factors that either increase the forces applied to regions of the lung (e.g., surfactant dysfunction, heterogeneous ventilation due to atelectasis and flooded alveoli, repetitive opening and collapse of alveoli) or weaken lung tissue (such as age, inflammation) predispose to injury. In addition, factors that prime the inflammatory response or inhibit tissue healing also increase the lung’s susceptibility to VILI [25], as does genetic predisposition. It is thought that the interaction of mechanical ventilation with other coexisting lung abnormalities is one explanation as to why identical ventilation settings produce VILI in some individuals but not all.

Is the mechanism of ventilator-induced injury due solely to physical disruption due to excessive force?

Most of the investigations cited above suggest physical disruption of the lung (e.g., capillary stress failure by alveolar overdistention) as one mechanism whereby mechanical ventilation produces lung injury. However, evidence of a potentially important role for ventilator-induced molecular and cell-mediated events in the pathogenesis of ventilator-induced injury soon began to emerge.

In 1983 Hamilton et al. [26] (N=263) published a study showing a benefit of high-frequency oscillation (i.e., using 15 Hz, V\textsubscript{i} 1.5 ml/kg; mean airway pressure 15 cmH\textsubscript{2}O) compared to “conventional” ventilation (using PIP 25 cmH\textsubscript{2}O; PEEP 6 cmH\textsubscript{2}O) in surfactant depleted rabbits. In this study the authors found significantly better lung function with fewer signs of histological lung injury in the high-frequency oscillation study group than in the conventional ventilation group. On further analysis, however, the investigators noted the presence of granu-
locyte infiltration in the alveoli and interstitium of the rabbits in the conventional ventilation group. To determine whether the granulocytes had a significant role in producing ventilation related lung injury Kawano et al. [27] (N=126) repeated the study using both neutrophil-depleted rabbits and neutrophil-depleted rabbits in which the granulocytes were reintroduced. They found that in contrast to rabbits with neutrophils, the neutrophil-depleted rabbits did not develop significant lung injury (changes in oxygenation, vascular permeability, hyaline membranes or granulocyte infiltration) with conventional ventilation. However, when neutrophils were re-infused into the neutrophil depleted rabbits, lung dysfunction ensued. Thus lung injury due to surfactant dysfunction/VILI in this model was not due simply to structural disruption but was mediated in large part by granulocytes.

Other investigators have observed that ventilation of lungs can increase levels of inflammatory mediators within the lungs, and that treatment with blockers of inflammatory mediators can reduce ventilator associated lung injury. For example, Tremblay et al. [28] (N=364) found increased bronchoalveolar lavage levels of several inflammatory mediators—including tumor necrosis factor (TNF) a, interleukin (IL) 6, and IL10—in ex vivo rat lungs subjected to injurious ventilation strategies. The same investigators in another report [29] (N=75) coined the term “biotrauma” to encompass this new field of investigation of molecular and cell mediated mechanisms of VILI. Supportive of this hypothesis, investigators such as Narimanbekov and Rozycki [30] (N=52) demonstrated that use of cytokine modulators can reduce lung dysfunction following mechanical ventilation. Administration of an IL-1 receptor antagonist prior to initiation of the injurious ventilation strategy in surfactant depleted rabbits reduced the severity of lung injury (bronchoalveolar lavage levels of polymorphonuclear cells, elastase, and albumin) produced by hyperoxia and 8 h of ventilation with 24 cmH2O PIP. Of note, in this study the use of IL-1 receptor antagonist (RA) did not significantly improve either lung compliance or oxygenation. Other investigators, however, have demonstrated reduced ventilator associated lung injury as well as reduced ventilator-associated systemic abnormalities (such as increased gut permeability) using mediators such as anti-TNF or transgenic mice strains (for a concise summary of these studies see [31]).

Numerous subsequent studies have revealed species and model-specific differences with regards to levels of multiple mediators (including cytokines, receptors, ion channels, proteases, and extracellular components such as collagen/laminin) as well as a role for various cell types in addition to neutrophils in mediating the ventilator associated inflammatory response (e.g., type II pneumocytes, macrophages). Studies have also suggested that mechanotransduction (the conversion of externally applied forces on cells into activation of various cell signaling pathways and alterations in gene expression or cell structure) plays a role in VILI, and multiple stretch-activated signal transduction pathways (e.g., mitogen-activated protein kinases, stretch-sensitive ion channels, integrin receptors) have been identified. In a seminal study using an isolated perfused rat lung model Parker et al. [16] (N=51) abrogated the increase in microvascular permeability due to high PIP ventilation (20 and 30 cmH2O) with gadolinium (an inhibitor of endothelial stretch-activated cation channels). In a subsequent study Parker et al. [17] demonstrated in the same model that inhibition of phosphotyrosine kinase increases the susceptibility of the lungs to high PIP injury; in contrast, inhibition of tyrosine kinase attenuates lung injury. The results of these studies lent further support to the contention that ventilation-induced changes in microvascular permeability is actively modulated by a molecular response to ventilation rather than simply a result of passive structural failure of the alveolar capillary membrane.

Not surprisingly, significant debate has ensued and continues as to the relative contribution of physical disruption vs. biotrauma in the pathogenesis of ventilator-induced injury [32, 33].

Is ventilator-induced injury limited to the lung?

Early investigators appreciated that in addition to lung injury, mechanical ventilation can also have adverse systemic sequelae including death from tension pneumothorax, or hypotension and impaired renal function secondary to high PEEP. In recent years experimental evidence has emerged that mechanical ventilation may also produce numerous other systemic sequelae. For example, Kolobow et al. [34] (N=378) compared the effect in sheep of ventilation with prolonged high Vt (50–70 ml/kg, PIP 50 cmH2O) to that with low Vt (10 ml/kg, PIP 15–20 cmH2O). Interestingly, they found that all sheep subjected to the high Vt strategy died with multiple organ system dysfunction within 48 h.

In 1998 we hypothesized that biotrauma and the translocation of mediators can lead to the development of multisystem organ dysfunction [35] (N=185). Supportive of this hypothesis, several investigators have demonstrated that the increased alveolar capillary membrane permeability observed with high Vt ventilation allows translocation of various alveolar inflammatory mediators or bacteria into the systemic circulation. For example, using in an isolated perfused lung model von Bethmann et al. [36] (N=122) showed that high Vt ventilation produces increased levels of TNFα and IL6 in the perfusate; and in an acid aspiration rat model Chiumento et al. observed increased serum TNF-α levels in the group ventilated with zero PEEP and high Vt [37] (N=130). Similarly, using an in vivo dog model Nahum et al. [38] (N=85) demonstrated translocation of Escherichia coli from the lungs into the
bloodstream of most dogs ventilated with high Vt and low PEEP (transpulmonary pressure of 35, equivalent to 76 ml/kg, 3 cmH2O PEEP). In contrast, bacterial translocation was only found in one of six dogs ventilated at the same end-inspiratory pressure (35 cmH2O) and 10 cmH2O PEEP, and in none of the dogs ventilated with Vt 15 ml/kg and 3 cmH2O PEEP. Subsequent studies have provided further evidence of ventilation-induced “spillover” of a number of other intra-alveolar pathogens (e.g., Klebsiella [39], LPS [40]) and inflammatory mediators into the circulation. In addition, recent studies have shown that ventilatory strategy can also have a wide range of effects on remote organs, including increased ileal permeability [41], increased renal and small intestine apoptosis [42], changes in the peripheral immune response and host susceptibility to infection, and the development of systemic capillary leak [32, 43].

Strengths and weakness of the bench studies

As alluded to above, bench studies have a number of limitations that prevent direct extrapolation to the clinical arena. Although in vitro and ex vivo models are indispensable for addressing questions regarding the effect of cell stretch or ventilation on particular cells or signal transduction pathways in the absence of confounding systemic sequelae (such as hypotension due to high mean pleural pressure), the findings from such models may not be representative of the events occurring in vivo. In addition, although animal models may minimize differences between study participants, there are genetic and species-specific susceptibilities and responses to certain stimuli which may or may not be representative of the human response. Furthermore, with few exceptions the majority of laboratory studies of VILI to date have involved only brief periods of ventilation (hours) and used fairly extreme ventilatory settings to produce injury, leading some to question the clinical relevance of such studies.

Seminal bedside studies on ventilation-induced lung injury

From a clinician’s perspective the key question is whether VILI contributes to patient morbidity and mortality, and if so, how can it be avoided. Although underlying lung injury is known to be a confounding factor present in many patients on ventilatory support, the laboratory studies have suggested that, if anything, this places the patients at increased risk of VILI as: (a) these patients often require higher pressure/volume to oxygenate/ventilate, and (b) many of these patients have factors known to increase susceptibility to VILI (such as surfactant dysfunction, malnutrition, endotoxemia).

In a series of publicationsGattinoni et al. used computed tomography to demonstrate the effect of different ventilation strategies on the lungs of patients with acute lung injury (ALI). In a highly cited study Gattinoni et al. [44] (N=318) examined the effect of ventilation with different levels of PEEP (5, 10, and 15 cmH2O) on lung compliance, lung volumes (as measured by helium dilution), and the computed tomographic appearance of the lungs in 20 patients with ALI. The key finding of this study was the visual evidence that lung inflation in ALI is extremely heterogeneous, with dependent regions being flooded or atelectatic, and often only a low volume of aerated nondependent lung. In addition, ventilation in these patients with ALI appears to be distributed primarily to this low volume of aerated nondependent lung with relatively normal compliance (which the authors termed “baby lung,” due to its low volume) [44, 45]. These computed tomography studies also suggested that the pressure-volume curve of the patients is representative of only the healthy aerated zones of the lung, and that optimal lung recruitment (i.e., opening up of lung units without significant overdistension) coincides with the PEEP at which optimal lung compliance was measured. Thus, in keeping with the speculations of Webb and Tierney [10] and others decades earlier, the studies by Gattinoni et al. demonstrated how mechanical ventilation of heterogeneously injured lungs with even relatively low Vt can produce significant regional overdistension. For example, in a lung with only 25% of alveoli ventilated, a ventilator set to deliver a Vt of 10 ml/kg would actually deliver approx. 40 ml/kg to the patient’s “baby lungs”—a volume associated with significant lung injury in laboratory studies.

Based on the above, and mounting experimental evidence of potential adverse sequelae of mechanical ventilation with greater than physiological volumes, clinical investigators began to question whether mechanical ventilation using “conventional” Vt of 10–15 ml/kg to maintain normal arterial oxygenation and ventilation is necessary or harmful, particularly in patients with ARDS and “baby” lungs. After all, in patients with status asthmaticus a ventilatory approach that uses lower peak pressures and allows higher PaCO2, a technique termed “controlled hypoventilation,” appeared to be well tolerated and associated with improved outcomes [46, 47].

In 1990 Hickling et al. [48] (N=368) published a landmark study showing that the use of a “protective” ventilation strategy that limits PIP (<40 or <30 cmH2O if possible, corresponding to Vt of 4–7 ml/kg) and allowed hypercapnia and a slight deterioration in oxygenation, appeared to reduce mortality by 60% in 70 patients with severe ARDS compared to mortality predicted by Acute Physiology and Chronic Health Evaluation II score (i.e., 16% vs. 40%). This seminal study suggested a promising new approach for ventilation in ARDS. A major weakness of the study, however, was the absence of a concurrent
control group. In addition, the study was only a retrospective case series from a single institution, which despite showing an apparent survival advantage did not observe a difference in either gas exchange or signs of lung injury between survivors and nonsurvivors. These weaknesses, however, do not diminish the importance of this study which helped to change the prevailing philosophy at the time that normal arterial blood gases should be a major goal of ventilatory support.

To circumvent the inherent limitations of retrospective and nonrandomized trials, prospective randomized trials examined whether a ventilation strategy with lower vs. higher lung volume improves patient outcome. In 1995 Amato et al. [49] (N=238) published a positive trial that further fueled debate. In this study 28 patients with ARDS were randomized to either a low Vt/high PEEP strategy (Vt <6 ml/kg, PIP<40 cmH2O, permissive hypercapnia, PEEP 15–20 cmH2O, and a goal of a plateau pressure, Pplat <30 cmH2O) or a high Vt strategy (Vt 12 ml/kg, PEEP 6–8 cmH2O, Pplat of approx. 46 cmH2O). The low Vt strategy was associated with improved survival (40% relative reduction in mortality at 28 days). The benefits of the low Vt/high PEEP strategy were confirmed by extending the study to 53 patients at which point the study was stopped because an interim analysis revealed a significant survival difference (28-day mortality of 38% with the low volume/high PEEP strategy vs. 71% with the high Vt strategy; p<0.001) [50] (N=678). In addition to a survival advantage, at 28 days more patients in the “protective” ventilation strategy arm had been weaned from ventilation (66% vs. 29%), and there was a lower incidence of barotrauma (7% vs. 42%). However, the Amato et al. study was criticized for having higher than predicted mortality in the control group. Furthermore, three other small prospective randomized trials failed to find a survival advantage of low vs. high Vt ventilation strategy [51, 52, 53] (N=258, 182, 102, respectively). These smaller negative trials, however, were criticized for having only a small difference in Vt between study groups, insufficient statistical power to detect a difference, the presence of uncorrected acidosis in the low volume arms, as well as the fact that the conventional ventilation arms in all the negative trials had a Pplat less than 32 cmH2O (i.e., had relatively low end-inspiratory lung volumes more in keeping with ventilatory strategies found to be noninjurious in laboratory studies).

To overcome the limitations of these small studies the National Institutes of Health (NIH) sponsored a consortium (ARDSNet) to carry out a large multicenter prospective randomized trial in which patients with ALI or ARDS were randomized to either: (a) “traditional” Vt of 12 ml/kg predicted body weight (using a formula based on gender and height rather than actual weight) and a Pplat of 50 cmH2O or lower, or (b) Vt of 6 ml/kg predicted body weight and a Pplat of 30 cmH2O or lower [54] (N=1027). Although the study was conceived with a patient population of approx. 1000, the trial was stopped early after an interim analysis revealed a 22% relative survival advantage with the low Vt strategy (n=861; mortality of 31% vs. 39.8%). In addition to improved survival, patients in the low Vt strategy were also found to have more days free of ventilatory support during the 28 days following randomization (12±11 vs. 10±11). Of note, the mean Pplat of the low and high Vt strategy were 25±6 vs. 33±8 cmH2O respectively (a greater difference between groups than that of the small, negative trials). Furthermore, in keeping with the animal studies suggesting that ventilation affect systemic inflammation, the low Vt strategy also resulted in lower plasma IL-6 levels (on day 3) as well as fewer nonpulmonary organ failures (circulatory, renal, coagulation).

Subsequent reports, however, have brought to light a number of caveats regarding the ARDSNet study. First, some have argued that the study demonstrated the increased mortality of a high Vt strategy resulting in a high Pplat (33 cmH2O) rather than a survival advantage to using Vt of 6 ml/kg. Of note, the Pplat in all of the smaller negative studies was less than 32 cmH2O in both study groups (i.e., control and less injurious ventilation strategy groups). Second, it has been argued that those in the low Vt group may have developed higher auto-PEEP than those in the conventional ventilation group due to the high respiratory rates used [55]. As such, the survival advantage may have been due to higher PEEP rather than low Vt and/or end-inspiratory lung volume (although the results of a more recent trial argue against this [56]). Third, the study population was restricted to patients with ALI or ARDS and the exclusion criteria included patients with severe chronic respiratory disease, morbid obesity, burns, a contraindication to hypercapnia or hypoxia (such as increased intracranial pressure or sickle cell disease) or a predicted 6 month mortality of more than 50%. Thus the study findings cannot be directly extrapolated to the excluded patient populations or to patients with less injured or normal lungs. Fourth, the low Vt group developed hypercapnia and received bicarbonate to treat acidosis (note: bicarbonate was not used in the smaller negative trials). Thus it is unclear to what extent bicarbonate contributed to the survival difference. Fifth, the higher number of ventilator-free days was due to reduced mortality (i.e., no significant difference was found in ventilator-free days among survivors between the two groups). Nevertheless, despite these limitations this study was the only large interventional study in decades in ARDS patients to show a significant reduction in mortality, and certainly was in keeping with the plethora of laboratory studies showing that high volume lung ventilation strategies are deleterious. Thus this study provided a new “gold standard” ventilation strategy for patients with ARDS or ALI.

Another seminal study in patients that also supported the experimental evidence that ventilation strategy can
have systemic effects on the host inflammatory response was published by Ranieri and colleagues [57] (N=360) in 1999. This study, entitled the “Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome—a randomized controlled trial,” examined whether a lung protective ventilation strategy in patients with ARDS reduces their pulmonary and systemic inflammatory cytokine response. Fifty-one ARDS patients who had been ventilated for less than 8 h were randomized to either “control” ventilation (Vt 11 ml/kg to produce normal PaCO2) and PEEP (6 cmH2O) producing best improvement in PaO2 without worsening hemodynamics; Pplat 31 cmH2O) or Vt and PEEP based on the pressure-volume curve (Vt 7 ml/kg, PEEP 15 cmH2O, Pplat 25 cmH2O). In the 44 patients who completed the study the concentration of inflammatory mediators 36 h after randomization was found to rise significantly in the control group (i.e., bronchoalveolar lavage levels of IL-1β and IL-6 and as well as bronchoalveolar lavage and plasma levels of TNF-α, IL-6, TNF-α receptors, and IL-1 RA) whereas in patients in the lung-protective strategy group a reduction in bronchoalveolar lavage concentrations of polymorphonuclear cells, IL-1β, TNF-α, IL-8, IL-6, TNF-α receptors, IL-1 RA, and in plasma concentration of IL-6, IL-1 RA, and a TNF-α receptor was found. Of note, this study was not designed to address whether these changes in inflammatory mediators resulted in improved survival or long-term outcomes (i.e., the ventilation protocols were only set for 36–40 h post inclusion, and organ failure and mortality were not primary outcomes). However, a post-hoc analysis revealed more ventilator-free days (over 28 days) in the lung protective group, and a number of subsequent clinical studies have also demonstrated ventilation strategy dependent changes in systemic inflammatory mediators (including the previously discussed NIH trial [54, 58]). Of importance, although there appeared to be an association between mediator levels and patient outcome in several studies, a cause and effect relationship has never been demonstrated.

Recently the NIH consortium published the results of yet another large trial comparing the effect of high vs. low PEEP on lung injury and survival in patients with ARDS. In this study 549 patients with ALI or ARDS were randomized to ventilation with Vt of 6 ml/kg, Pplat of less than 30 cmH2O, and PEEP of either 8.3±3.2 or 13.2±3.5 cmH2O [56]. The study was stopped early due to futility when an interim analysis revealed no significant differences in either mortality or ventilator-free days in the 28-day period following randomization. Thus, key clinical questions including how much PEEP is ideal, and what is the best way to determine optimal PEEP remain unanswered.

Similarly, to date most of the other promising interventions found to reduce lung injury and improve outcome in animal studies (e.g., prone positioning, surfactant supplementation, nitric oxide, lung recruitment maneuvers) have not been found significantly to improve patient survival or outcome in adult intensive care patients [59, 60, 61, 62]. As such, ongoing investigations at both the bench and bedside continue in the hopes of addressing the reasons for the discrepancies and better understanding the complex interactions of ventilation with the lung/whole organism.

In summary, the study of VILI over the past century exemplifies the “bench to bedside and back to the bench” research approach. This review discusses several of the seminal studies that led to our current understanding of VILI. Understanding these studies is helpful for interpreting and applying current guidelines for ventilation as well as appreciating the need for further studies at both the bench and bedside to define the precise mechanisms of injury and develop novel approaches to further reduce or abrogate ventilator-induced injury.

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Acute lung injury and the acute respiratory distress syndrome: a clinical review

Arthur P Wheeler, Gordon R Bernard

Acute respiratory distress syndrome and acute lung injury are well defined and readily recognised clinical disorders caused by many clinical insults to the lung or because of predispositions to lung injury. That this process is common in intensive care is well established. The mainstay of treatment for this disorder is provision of excellent supportive care since these patients are critically ill and frequently have coexisting conditions including sepsis and multiple organ failure. Refinements in ventilator and fluid management supported by data from prospective randomised trials have increased the methods available to effectively manage this disorder.

Definition and diagnosis

Acute respiratory distress syndrome and acute lung injury were first described in 1967, and are characterised by the abrupt onset of clinically significant hypoxaemia with presence of diffuse pulmonary infiltrates. These infiltrates show on radiograph (figure) as pulmonary oedema resulting from increased pulmonary vascular permeability. These disorders affect patients of all ages and usually happen soon after an easily identified triggering event (panel 1). The likelihood of developing acute lung injury depends on the predisposing disorder; some events (eg, severe sepsis) are more likely to progress to lung injury than others. The risk of individuals developing acute lung injury also depends on patients’ characteristics. For example, alcoholism is a predisposing factor and data now suggest the possibility of a genetic predisposition. Although the causes of acute lung injury have been segregated into direct and indirect injuries, outcomes are similar in both categories if age, underlying chronic illnesses, and severity of non-pulmonary illness and gas-exchange abnormalities are controlled for.

When the hypoxaemia in acute lung injury is severe (partial arterial pressure of oxygen [PaO₂]/fractional concentration of oxygen in inspired air [FIO₂] <200), the disorder is termed the acute respiratory distress syndrome. However, most epidemiological and interventional studies use the broader range of gas-exchange abnormality (PaO₂/FIO₂ <300) and refer to the overall disorder as acute lung injury. These definitions have limitations: for example, the physiological thresholds do not need standardised ventilatory support. The use of positive end-expiratory pressure (PEEP) can improve oxygenation indices sufficiently to convert patients meeting the definition of acute respiratory distress syndrome to have acute lung injury, and can change the physiology in the lung such that the patient does not meet the criteria for acute lung injury or acute respiratory distress syndrome. Another factor that affects the definition of acute respiratory distress syndrome is the substantial variability of physicians’ interpretations of radiographs. Nevertheless, this nomenclature developed by international consensus is nearly a decade old and is widely accepted.

For consistency and clarity we use the inclusive term acute lung injury for the remainder of this Review.

Because acute lung injury has no pathognomonic laboratory or radiographic feature, diagnostic confusion could occur with other diseases that cause hypoxaemia and show pulmonary oedema on radiographs (panel 3). Although the term acute lung injury helps to identify a group of patients who can generally be treated in the same way, there are important exceptions. For example, several rare diseases (eg, acute eosinophilic pneumonia) do have a specific treatment and, if not carefully considered, could be overlooked under the general classification of acute lung injury. Clinicians should carefully think about all patients meeting the definition of acute lung injury to ensure that they do not miss an underlying disease with a specific treatment.

Left atrial hypertension from either intravascular volume overload or heart disease (eg, mitral stenosis, left ventricular failure) most often present the diagnostic dilemma. Historically, efforts have been made to distinguish acute lung injury from hydrostatic pulmonary oedema by measuring pulmonary vascular permeability in research settings and by measuring pulmonary-artery occlusion pressure in clinical settings. The distinction between these two disorders was thought to be especially important for patients entering clinical studies, but this measurement has mainly been abandoned with the realisation that exceeding an arbitrary pulmonary-artery occlusion pressure does not exclude a diagnosis of acute lung injury since a concurrent illness could raise this

Search strategy and selection criteria

We searched the Cochrane Library and MEDLINE (for entries up to October, 2005). We used the search terms “acute lung injury”, “ALI”, “acute respiratory distress syndrome”, and “ARDS”. Animal and human studies were reviewed. We mainly selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search and selected those we judged relevant. Generally, preference was given to large randomised human clinical trials, but several review articles, letters, and editorials were included because they provided a comprehensive overview of histopathology or a historical view of treatment. The reference list was subsequently modified during the peer-review process on the basis of comments from reviewers and updated with newer publications.

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pressure. Such a situation could happen in a patient with pneumonia-induced septic shock, diffuse bilateral pulmonary infiltrates, and refractory hypoxaemia who has undergone large-volume fluid resuscitation. In this setting, pulmonary-artery occlusion pressure could well exceed 18 mm Hg, although the patient would still have acute lung injury. Additionally, without great diligence, measurements of bedside pulmonary-artery occlusion pressure do not have the precision needed to make this distinction, because they vary greatly.\(^{12,13}\) Even when pulmonary-artery occlusion pressure is less than 18 mm Hg, one cannot confirm that oedema is the result of altered permeability because reduced colloid oncotic pressure promotes oedema in the absence of permeability changes.\(^{14,15}\)

Prevalence and outcomes

Depending on how the syndromes are defined and where the survey is undertaken, the reported frequency of acute lung injury varies widely. The frequency seems to be increased in developed countries and if less stringent criteria for hypoxaemia are used. Estimates worldwide range from 1·5 to 75 cases per 100 000 population.\(^{16,17}\) Irrespective of differences in estimates, hundreds of thousands of cases occur worldwide every year and are associated with substantial morbidity, cost, and mortality.\(^{18,19}\)

Mortality rates of acute lung injury also vary greatly depending on the age of the patient and presence of non-pulmonary organ dysfunctions; advanced age, shock, and hepatic failure are most predictive of death whereas young trauma patients have the best outcomes.\(^{20}\) Paradoxically, for a disease known predominantly to cause hypoxaemia, the initial degree of gas-exchange impairment is a poor predictor of outcome unless severe (eg, PaO\(_2\)/FIO\(_2\) <50).\(^{7,21}\) Severe hypoxaemia that persists for days has a greater predictive value.\(^{22}\) Two decades ago, mortality from acute lung injury was often reported as 50–70% but has since declined over time.\(^{23}\) Reasons for this improvement are unknown; however, advances in supportive care are thought to have decreased extrapulmonary organ failures, which could account for most of the change.\(^{24}\) In the most recent randomised trials,\(^{25}\) overall 28-day mortality is reported as 25–30% whereas mortality in community-based surveys is 35–40%.

For most patients with acute lung injury, outcome is determined in 7–10 days, by which time about half of patients have died or have been weaned off treatment.\(^{26}\) Nevertheless, a substantial proportion have a slow recovery, with up to 10% of patients needing more than 1 month of ventilation. Data suggest that the survival for patients with persistent, severe acute lung injury could be much better than previously thought, with survival rates near to 70%.\(^{27}\) Lung function in survivors of acute lung injury returns to normal over 6–12 months\(^{28}\) but recovery of lung function is probably not the most important problem. Neuropsychiatric problems and neuromuscular weakness are now known to happen frequently and often delay return to school or work by months and can occasionally be permanent.\(^{29,32}\)

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Panel 1: Causes of acute lung injury

**Direct injury**
- Pneumonia
- Gastric aspiration
- Drowning
- Fat and amniotic-fluid embolism
- Pulmonary contusion
- Alveolar haemorrhage
- Smoke and toxic gas inhalation
- Reperfusion (pleural effusion drainage, embolectomy)
- Unilateral lung re-implantation

**Indirect injury**
- Severe sepsis
- Transfusions
- Shock
- Salicylate or narcotic overdose
- Pancreatitis
Histopathology
Early acute lung injury is characterised histologically by a diffuse neutrophilic alveolar infiltrate, with haemorrhage, and the accumulation of a protein-rich pulmonary oedema. During this acute, so-called exudative phase, a panoply of cytokines (eg, tumour necrosis factor, interleukin 1, interleukin 8) incites and perpetuates inflammation. By increasing oxidant stress and protease activity, the inflammatory mixture in the alveoli and interstitium reduces surfactant production, and inactivates remaining surfactant, thereby promoting widespread atelectasis. Additionally, elastases damage the structural framework of the lung, and both alveolar-capillary and epithelial-cell injury can be seen. Damage of the epithelial barrier exacerbates the tendency for alveolar flooding, and delays recovery by impairing fluid clearance. A procoagulant tendency is seen in the lung as concentrations of anticoagulant proteins (protein C, protein S) fall and expression of procoagulant proteins (tissue factor) and anti-fibrinolytic proteins (plasminogen activator inhibitor 1) increases. Together, these changes are probably responsible for capillary thrombosis.

Afterwards, some patients with acute lung injury have a fibroproliferative phase, during which chronic inflammation, fibrosis, and neovascularisation take place. Unfortunately, this phase has no specific features, apart from time that allows the clinician to distinguish the exudative period from the fibroproliferative period. We do not know why most survivors rapidly resolve the acute inflammation but some progress to the chronic phase. Another mystery is why the histological changes of fibroproliferation can be seen in some patients in days, but not occur in others for weeks.

Pathophysiology
In the early phase of acute lung injury, leakage of oedema fluid into the lung and inflammatory cellular infiltrates cause diffusion abnormalities and ventilation-perfusion mismatch, which clinically manifest as hypoxaemia. Concurrently, cellular infiltration, diffuse atelectasis, and oedema fluid reduce thoracic compliance. The combination of regional alveolar over-distention and small-vessel thrombosis increases dead space. Hypoxaemic vasoconstriction and capillary obliteration raise pulmonary-artery pressures, and if raised pressures are sustained, cor pulmonale can occur. Increased dead-space ventilation, reduced lung compliance, and hypoxaemia combine to greatly increase the effort of breathing. Eventually, oxygen demands exceed ventilatory capability, and hypoxaemic, hypercarbic respiratory failure will take place if left untreated.

Treatment
Acute lung injury has no specific treatment, although some doctors would argue that ventilation with a normal tidal volume, which results in reduced airway pressure, is a specific treatment. The mainstay of treatment is supportive care, mainly to avoid iatrogenic complications and treat the underlying cause, while maintaining adequate oxygenation. Almost all patients with acute lung injury need positive-pressure ventilation with supplemental oxygen and PEEP. Physical support is usually provided by use of a cuffed tracheal tube. Although some patients can be successfully supported with non-invasive mask ventilation, few large, well conducted randomised trials demonstrate the feasibility of non-invasive ventilation or indicate its benefits over tracheal-tube-delivered ventilation.

Supportive care
A treatment for the cause of acute lung injury is desirable. Measures for the prevention of deep vein thrombosis, gastrointestinal bleeding, and pressure ulcers should be provided for all patients. The head of the bed should be raised to an angle of at least 30° to reduce the risk of hospital-acquired pneumonia, probably for all patients, but at least for those who are enterally fed. Although enteral nutrition is widely advocated, few data are available to guide selection of the formula; optimum delivery location; timing of initiation, rate of administration, and clinical practice is highly heterogeneous. All invasive catheters should be inserted with maximum barrier precautions and chlorhexidine skin preparation. Standardised, goal-directed sedation practices are sensible because they decrease the length of mechanical ventilation and intensive care unit stay. Glucose control that is more stringently than is traditionally maintained could be beneficial, although this strategy has not been tested exclusively in patients with acute lung injury.
Mechanical ventilation, oxygen, and PEEP

Few of the many combinations of ventilatory mode, rate, tidal volume, flow rate and pattern, F_{O_2}, and PEEP, have undergone rigorous testing in human beings with durable, clinically important endpoints such as mortality. Therefore, how to best ventilate and oxygenate patients with acute lung injury is controversial. Historically, the primary goal was to achieve near normal arterial blood gases, even if high tidal volumes and minute ventilations had to be used.\(^5\)\(^6\) Arterial blood gases were obtained frequently to monitor treatment in some patients after each ventilator change. In this traditional approach, the risks of airway pressure were perceived as small because the complications of high airway pressures (eg, pneumothorax), were believed to be uncommon, readily apparent, unavoidable, and easily treated.\(^7\) Tidal volumes that were 50–100% larger (10–15 mL/kg of actual bodyweight) than those of spontaneously breathing healthy controls at rest (5–7 mL/kg predicted bodyweight) would normally have been provided.\(^4\)\(^5\) Supplemental oxygen was supplied, usually with low PEEP, and when the required oxygen concentration reached a value that prompted physician concern, PEEP was increased to maintain an acceptable PaO\(_2\), at an acceptable F_{O_2}. The definition of acceptable differed by physician but there was some consensus that PaO\(_2\) greater than 60 mm Hg with F_{O_2} less than 0.6 mm Hg were desirable.\(^10\)\(^11\) Heterogeneity in selection of tidal volume, and positive end expired pressure-F_{O_2} combinations existed because few data were available to guide choices.\(^12\) Wide variations in reported practices continue today.\(^5\)\(^13\)

In the past 5 years, advances have been made in the ventilation of patients with acute lung injury, which centre on three issues: the realisation that alveolar involvement is heterogeneous, awareness that the bodyweight of many patients is substantially larger than predicted, and recognition that the damage caused by a ventilator when adjusted to maintain normal blood gases could be substantial but not immediately apparent. Lung CT scans of patients with acute lung injury showed the heterogeneous nature of alveolar effects. Imaging revealed that portions (typically dependent regions) of the lung were densely infiltrated, while other areas appeared normal or near normal.\(^5\)\(^13\) This finding suggests that the forcing of supra-normal, and perhaps normal, tidal volumes into the injured lung will result in over-distention and injury of the most compliant alveoli. Moreover, evidence has suggested that injury to normal alveoli could result from airway pressures traditionally thought to be safe. This notion was supported by animal studies indicating that alveolar overdistention can not only perpetuate, but can also cause lung injury, and gave rise to the idea that tidal volumes should be reduced to around the smaller volume of aerated lung in acute lung injury (ie, the baby lung).\(^26\)\(^27\) Furthermore, animal studies showed that the injury from the large tidal volume was not simply a mechanical event of tearing alveoli, but rather that high-volume ventilation led to local and systemic inflammation, sometimes referred to as biotrauma.\(^31\)

Lung capacity is predominantly affected by age, sex, and height, yet tidal volume was customarily indexed to actual bodyweight. With the recognition that patients from the intensive care unit were, on average, nearly 20% larger than their ideal bodyweight, traditional tidal volumes were probably too large and should be reduced to at least those appropriate for age, sex, and height.\(^62\) This finding led to the decision by some investigators to index tidal volume to predicted bodyweight, a potentially important decision to prevent barotrauma.

Several animal studies confirmed that high airway pressures applied to healthy lungs caused rapid histopathological changes identical to those seen in human beings with acute lung injury and could lead to systemic inflammation and extrapulmonary organ damage. This finding has been confirmed in human studies and remains the leading theory to explain how lower tidal volume ventilation reduces extrapulmonary organ failures and improves survival rates. Additionally, data now suggest that mechanically ventilated patients without acute lung injury have an increased likelihood of developing lung injury with large tidal volumes.\(^63\)

Animal studies of lung injury have also shown that smaller tidal volumes were associated with reduced oedema formation\(^44\) After these studies, several case series suggested potential benefit of smaller tidal volumes in various lung diseases.\(^65\)\(^66\) Four small randomised trials examined the practice of reduced tidal volume ventilation in patients with, or at risk of, acute lung injury. Three\(^65\)\(^66\) of these studies failed to show benefit of lower tidal volume ventilation. The fourth study\(^67\) used a more complex approach than the other three, by testing the lower inflection point of lung compliance (Pf\text{flex}) to set PEEP, undertaking recruitment manoeuvres (sustained increases in ventilator pressure), and using ventilation with smaller tidal volumes. This study\(^67\) showed a striking survival benefit compared with a traditional approach, but was not conclusive because of: its small size; the technical difficulty of Pf\text{flex} measurement; the high mortality rate in the control group; and the fact that many patients studied had an uncommon cause of lung injury.

The US National Institutes of Health Network for Acute Respiratory Distress Syndrome (NIH ARDS Network) investigated whether lower tidal volume ventilation was beneficial by undertaking a large randomised multicentre study\(^68\) of volume-assisted controlled ventilation, which compared a traditional tidal volume (12 mL/kg of predicted bodyweight) with a smaller tidal volume (6 mL/kg of predicted bodyweight). In both groups, breath size was indexed to predicted bodyweight, and plateau pressure limits mandated
additional tidal volume reductions if those pressure limits were exceeded. PEEP and FIO2 were set by use of an arbitrary, but prospectively defined, scale to achieve an arterial saturation of 88–95% or PaO2 of 55–80 mm Hg. When this strategy was applied, rapid increases in respiratory rate, decreases in PaO2/FIO2, and modest increases in PaCO2 were often seen. Although these physiological changes seem to be adverse and a cause for concern, and continue to hamper the use of lower tidal volumes by some clinicians, the changes seem to be unimportant for most patients. This trial26 showed a significant reduction in 28-day mortality from 40% to 31%, with an increase in the number of days free of ventilation and extrapulmonary organ failure. This study also confirmed and built on previous findings that larger breaths were associated with a delayed resolution of the inflammatory response.73,74 This study26 has four notable differences from previous unsuccessful trials: it used the lowest tidal volume of all the trials; it linked tidal volume to predicted bodyweight; it had specific rules to treat respiratory acidosis, allowing the respiratory rate to increase to 35 breaths per min and buffering the acidosis with sodium bicarbonate if needed; and it was the largest study, allowing for detection of smaller survival differences.

This study has generated substantial debate,75–77 with some experts asserting that it was irrelevant because usual practice had already adopted lower tidal volumes. A few postulated that smaller volumes were beneficial only because the higher tidal volume was excessively high.78 Others theorised that reduction of tidal volume was not necessary if plateau pressures were below a safe threshold.79 Tidal volumes for 6 and 12 mL/kg was not necessary if plateau pressures were below a safe threshold.80–82 This finding provides strong evidence that use of reduced tidal volume is sensible, even when the initial plateau pressure is less than 30–32 cm H2O.

Results from published trials have not accorded with the hypothesis that both the tidal volume selections of 6 and 12 mL/kg of predicted bodyweight were suboptimum and that the best tidal volume lies either between these values or at less than 6 mL, but this theory is obviously the most difficult to test. If a consensus could be reached on mode and pulmonary end expiratory-FIO2 strategy, a study of tens of thousands of patients assigned to tidal volumes ranging from less than 6 mL/kg to almost 12 mL/kg would be needed to find the best tidal volume; such a study would not be feasible. The theory that the benefit of lower tidal volume resulted from tachypnoea-induced intrinsic PEEP is not supported by measurements of auto-PEEP in a large subset of enrolled patients,83 nor by data from a subsequent study of higher PEEP using the reduced tidal volume approach.84 Finally, no evidence supports the concern that patients ventilated with this lower tidal volume strategy needed more sedation or paralysis.

A pressure-limited mode of ventilation could be better than volume-cycled ventilation. A small randomised trial85 supports this notion, in which decreased extrapulmonary organ failures and mortality were seen with pressure-controlled ventilation. Unfortunately, the size of the study, baseline imbalances, and the very high mortality rate seen in the volume-ventilated group, call into question the generalisability of the results. Confirmation awaits additional large randomised controlled trials.86,87 No randomised controlled trials suggest that high-frequency ventilation improves survival of adult patients with acute lung injury,88–90 despite improving oxygenation.

Thus, we can conclude that use of smaller tidal volumes (6 mL/kg of predicted bodyweight) that is indexed to predicted bodyweight results in reduced markers of inflammation, higher survival, and fewer organ failures than traditional tidal volumes (12 mL/kg of predicted bodyweight). A key caveat is that tidal volume must be reduced even further if plateau pressures exceed 30 mm Hg.91 Although we need further investigation of mechanical ventilation strategies that improve outcomes, the ARDS Network study92 (the largest positive-ventilation trial undertaken) serves as a rational starting point for current clinical practice, and a benchmark against which future ventilation strategies should be tested.
Effects of PEEP
By recruiting atelectatic alveoli and increasing functional residual capacity of supine patients, PEEP reduces intrapulmonary shunting and improves oxygenation in many lung diseases. PEEP might also have detrimental effects: because it could increase the amount of lung water and, in some cases, PEEP could over-distend compliant alveoli and worsen ventilation perfusion matching, or even create dead space. Furthermore, by raising intrathoracic pressure, PEEP can decrease venous return and increase right-ventricular impedance, thereby causing hypotension.

Animal studies have shown that even low amounts of PEEP can reduce the development of ventilator-associated lung injury induced by high cyclic ventilator pressures. The known physiological benefits on oxygenation and the animal study results suggest that PEEP would improve the atelectasis of early lung injury and might even prevent development of acute lung injury in high-risk patients. Unfortunately, use of prophylactic PEEP has failed to show benefit in at least one large clinical trial. Nevertheless, some doctors do not believe the question of prophylactic PEEP has been resolved because the trial enrolled patients with various diseases at very different risks of acute lung injury, and used modest amounts of (8 cm H2O) of PEEP. Although not protective against the development of acute lung injury, a low amount of PEEP is given to most ventilated patients to prevent atelectasis.

In established acute lung injury, PEEP is routinely used to recruit the lung or prevent reversal of recruitment, thereby decreasing oxygen requirements, and improving other measures of lung function such as shunt fraction and compliance. PEEP titration to improve lung compliance or oxygen delivery has not shown any important clinical benefits. The range of clinical practice is wide and has included use of very high amounts of PEEP, which could be harmful.

To test the hypothesis that high amounts of PEEP would further increase the survival benefit of the lower tidal volume ventilation strategy, a large clinical trial was done in which all patients were ventilated with 6 mL/kg predicted bodyweight of tidal volume but were randomly assigned to receive treatment using the PEEP-FIO2 scale from the original trial, or using higher PEEP and lower FIO2 combinations. The approach of higher amounts of PEEP with a lower tidal volume was also used by Amato and colleagues, and incorporated recruitment manoeuvres in a subset of patients. In the first 4 days of the trial, although the higher PEEP group had higher pressure (14 mm Hg) than in the lower PEEP group (8 mm Hg), and oxygenation and lung compliance were better in the higher PEEP group, no benefit on survival, time on ventilator, or non-pulmonary organ function was shown. Furthermore, no benefit of higher PEEP was seen in patients with direct versus indirect injury, by severity of initial gas-exchange abnormality, or after adjustment for a possible imbalance in age of study participants between groups.

To explore the many reports of improved physiological variables after a recruitment manoeuvre, a subset of patients who had higher PEEP in this study were randomly assigned to receive 35–40 cm H2O continuous positive airway pressure for 30 s or a so-called sham recruitment manoeuvre. Unfortunately, neither striking nor lasting improvement was recorded in respiratory system compliance or oxygenation, but transient reductions were seen in blood pressure. The authors of this study did not exclude the possibility of benefit from other recruitment manoeuvre strategies and encouraged future studies.

However, the study of higher versus lower PEEP confirmed that when ventilated with 6 mL/kg predicted body weight, both groups had mortality rates of about 25%, as in the original lower tidal volume study. These results also suggest that in the range of values tested, higher concentrations of PEEP are probably not harmful. In view of these findings, we advocate use of 6 mL/kg predicted bodyweight tidal volume, and the lowest PEEP-FIO2 combination that produces acceptable oxygenation as a starting point for treatment. We do not advocate routine use of recruitment manoeuvres; however, recruitment manoeuvres are not unreasonable in patients with refractory hypoxaemia in an attempt to improve oxygenation.

Prose positioning and recruitment manoeuvres
Because most lung infiltrates are seen in dependent lung regions, it was postulated that prone positioning of patients redistributes blood flow and ventilation to the least affected areas of the lung, promotes secretion clearance; and shifts the weight of the mediastinal contents anteriorly, to assist in the recruitment of atelectatic regions. Animal and human studies suggest that lung compliance and alveolar recruitment, seen as infiltration on radiographs are improved by prone positioning. Additionally, animal studies suggest that prone positioning can restrict the degree of experimental lung injury. The practice was inexpensive and seemed to be safe with the possible exception of an increased risk of regurgitation and inadvertent extubation. Hence, many clinical studies of prone positioning in acute lung injury and other lung diseases were undertaken. Their findings consistently show that about two-thirds of all treated patients have a measurable improvement in oxygenation (PaO2/FIO2 ratio) shortly after prone positioning. Unfortunately, the improvement is often transient, and no study has shown that prone positioning improves important clinical outcomes such as survival, time on ventilation, or time in the intensive care unit.

Debate continues as to whether improved outcomes could be demonstrated by using larger studies, studying sicker patients, treating patients earlier, or by applying
prone positioning for a longer time each day, than has been done in previous studies. The failure to show a survival benefit from this practice could be because most patients with acute lung injury do not succumb to refractory hypoxaemia, but rather multiple organ failure. Therefore, measures improving oxygenation will probably prove important to survival only in a few patients. With current data, we do not advocate routine prone positioning of all patients but acknowledge that it might be a useful practice to boost oxygenation in a patient who is refractory to conventional treatment. Unfortunately, no recommendations can be offered on the optimum timing or duration of prone positioning until large randomised trials provide more information.

Corticosteroids

Many human trials suggest that treatment of patients at risk of acute lung injury with high doses of glucocorticoids does not decrease the frequency of the disease. Likewise, despite the striking inflammatory reaction in the alveoli, rigorous human studies suggest that high-dose glucocorticoids do not modify the course of acute lung injury when given early in the course of the disease. Despite failed studies of prevention or early treatment, great interest remains in the use of corticosteroids for the salvage of patients with persistent acute lung injury. Although this practice has often been regarded as treatment of the fibroproliferative phase, histological documentation of this is unusual. Several small uncontrolled studies suggest some clinical benefits of extended therapy with moderate-dose to high-dose glucocorticoids, including modification of the inflammatory response. Eventually, a small, prospective randomised crossover trial was undertaken, in which patients with acute lung injury that had persisted for more than 7 days were randomly assigned to placebo and 16 patients with the disease randomly assigned to high-dose methylprednisolone. Half of the patients assigned to placebo crossed over to methylprednisolone treatment because of failure to improve their lung injury score by one point or more, whereas no patient treated with corticosteroids crossed over to placebo. Analysis by intention to treat showed a significant reduction in mortality; per-protocol analysis showed no survival benefit. To reconcile this issue, the largest randomised, blinded trial so far of methylprednisolone versus placebo has been completed. Preliminary results have shown no difference in 60-day or 180-day mortality, despite improvements in gas exchange, blood pressure, and time on ventilator in patients given methylprednisolone. Conclusions from this study about the value of corticosteroids in late persistent acute lung injury will almost certainly be controversial. We do not recommend corticosteroids to prevent or treat early acute lung injury. Although data that show a survival benefit in the treatment of established acute lung injury are scarce, corticosteroids could offer some benefit with respect to gas exchange and haemodynamic stability.

Extracorporeal support

Extracorporeal membrane oxygenation and CO₂ removal have been attempted in patients with acute lung injury deemed refractory to conventional ventilatory support. Use of extracorporeal membrane oxygenation in children has been accepted as a useful support technology; however, it is rarely used in adults. Clearly, extracorporeal membrane oxygenation improves oxygenation, and extracorporeal CO₂ removal improves CO₂ clearance, but neither has been shown to improve survival or time on ventilation in controlled clinical trials. However, extracorporeal support has not conclusively shown outcome benefits and has been associated with substantial risks (eg, infection, bleeding) and costs, therefore, it cannot be recommended.

Fluid management

Animal and human data suggest that when lung-capillary permeability increases, lung water accumulates to a greater degree than usual at lower pressures of pulmonary-artery occlusion. Additionally, animal studies suggest that reduction of lung water improves oxygenation, and lung compliance. Human trials show improved physiological endpoints with various diuretic approaches to reduce lung water, including diuresis without vascular pressure measurement, intravascular pressure-targeted diuresis, and diuresis guided by direct measurements of lung water. However, abundant data suggest that prompt resuscitation of haemodynamically unstable patients improves outcome, whereas the same resuscitative efforts given later might not be helpful and could be harmful. These resuscitative protocols centre on fluid administration. In both the restrictive and liberal fluid-giving approaches, various endpoints have been used as therapeutic targets.

Therefore, does a conservative or liberal approach to fluid therapy alter outcomes, what are the optimum targets for resuscitation, and how should they be measured? A large randomised clinical trial has suggested no benefit of pulmonary-artery catheter insertion in patients with acute lung injury, but this trial has received criticism because they did not apply a specific protocol to guide use of catheter-derived data.

Vasodilators

Both non-selective (nitroprusside, hydralazine) and semi-selective (nitric oxide, prostaglandin E1, prostacyclin) vasodilators have been tested for the treatment of acute lung injury. Of these compounds, nitric oxide has been most widely studied, and like prone positioning, results are relatively consistent among studies: oxygenation and pulmonary vascular resistance are
improved, but those changes do not translate into better clinical outcomes.\textsuperscript{10–12} Based on existing data, routine use of nitric oxide or other vasodilators to treat acute respiratory distress syndrome cannot be recommended.\textsuperscript{13,14}

**Weaning from ventilation and other treatments**

For haemodynamically stable patients taking spontaneous breaths, who need less than 50% supplemental oxygen and less than 8 cm H\textsubscript{2}O PEEP, no method of weaning has been shown to be better than spontaneous breathing that is either unassisted or with a minimum level of pressure support. If a period of closely observed spontaneous breathing is successful, patients can be extubated.\textsuperscript{15–19}

Several other treatments have been used to either modify inflammation or change the mechanical properties of the lung with acute injury (panel 4). Unfortunately, none of these treatments has so far shown convincing improvements in outcomes in large controlled studies.

**Conclusion**

Acute lung injury and acute respiratory distress syndrome are common, costly, and potentially lethal diseases, for which treatment of the underlying cause is the first step to recovery. Prevention of nosocomial complications has an important role to achieve the optimum outcome. With respect to lung support, the only ventilatory practice proven to be beneficial in a large randomised trial is reduction of tidal volume to 6 mL/kg predicted bodyweight (or lower if needed), to achieve a plateau pressure of less than 30 cm H\textsubscript{2}O. This reduced tidal volume is coupled with use of the minimum F\textsubscript{I}O\textsubscript{2}-PEEP combination that is sufficient to achieve a saturation of 88–95% or a corresponding PaO\textsubscript{2}. Results from a large randomised study of fluid management suggest that conservative fluid use shortens time on ventilator and in the intensive care unit, but does not change survival.\textsuperscript{20}

**Conflict of interest statement**

GB and AW have been funded by the US National Institutes of Health, National Heart Lung and Blood Institutes ARDS Network. AW has been a funded investigator from the US NIH, National Heart, Lung, and Blood Institutes ARDS Network.\textsuperscript{21}

\textbf{References}


**Panel 4: Unproven treatments for acute respiratory distress syndrome**

- Ketoconazole\textsuperscript{33,35}
- Pentoxifylline and lisofylline\textsuperscript{32,34}
- Nutritional modification\textsuperscript{33,35}
- Antioxidants\textsuperscript{33,35}
- Neutrophil elastase inhibition\textsuperscript{18}
- Surfactants\textsuperscript{20,21}
- Liquid ventilation\textsuperscript{32,34}
- β-adrenergic agonists\textsuperscript{31,32}
- Nitric oxide\textsuperscript{33,35}


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Review


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Motor weakness in a patient in the intensive care unit (ICU) may be related to (1) pre-existing neuromuscular disorder that leads to ICU admission, (2) new-onset or previously undiagnosed neurological disorder, or (3) complications of non-neuromuscular critical illness. Neuromuscular syndromes related to ICU treatment consist of critical illness polyneuropathy, critical illness myopathy, and prolonged neuromuscular blockade, and are now recognized as a frequent cause of newly acquired weakness in ICU patients. Clinical features include quadriplegia, muscle wasting, and difficulty weaning from the ventilator. Evaluation of these patients is based on knowledge of
clinical setting and predisposing factors, focused neurological examination, detailed electrophysiological investigation, serum creatine kinase level, other laboratory studies as needed, and histological examination of muscle biopsy. If a central nervous system (brain or spinal cord) lesion is suspected, neuroimaging studies are required. In addition to conventional nerve conduction and needle electromyography, phrenic nerve conduction, diaphragm electromyography, blink reflex, and (recently) the technique of direct muscle stimulation have been employed. Critical illness polyneuropathy is an axonal motor and sensory neuropathy that often follows sepsis and multiorgan failure. Risk factors for critical illness myopathy are corticosteroids and neuromuscular blocking drugs, acute respiratory illness, and organ transplant. Three subtypes (acute necrotizing myopathy, thick myosin filament loss myopathy, and type II fiber atrophy) are recognized. Major differential diagnoses of critical illness related paralysis are incidental Guillain-Barré syndrome and unmasked myasthenia gravis. Rarely, atypical presentation of amyotrophic lateral sclerosis, polymyositis or other myopathies, and precipitation of porphyria or rhabdomyolysis due to drugs used in the ICU have been described. Recently a poliomyelitis-like flaccid paralysis due to West Nile virus infection was reported. A subgroup of patients with myasthenia gravis with muscle-specific tyrosine kinase antibody is noted to present as respiratory crisis. Muscle biopsy in ICU paralysis syndromes may be helpful in arriving at a specific diagnosis or to classify the type of critical illness myopathy. Nerve biopsy is only rarely indicated. Key words: critical illness polyneuropathy, critical illness myopathy, electrodiagnosis, flaccid quadriplegia, Guillain-Barré syndrome, intensive care, myasthenia gravis, neuromuscular disorders. [Respir Care 2006;51(9):1024–1040. © 2006 Daedalus Enterprises]

Introduction

Historically, neuromuscular disorders such as poliomyelitis, Guillain-Barré syndrome, myasthenia gravis, and amyotrophic lateral sclerosis (ALS) have been among the commonest causes of generalized and respiratory muscle weakness that require admission to the intensive care unit (ICU). Management of these patients with acute severe neuromuscular weakness in the modern ICU has led to substantial improvement in mortality and morbidity from these disorders. However, there has been increasing awareness of new onset neuromuscular weakness in patients with non-neurological critical illness. In 1984, Bolton et al described severe polyneuropathy in 5 patients with critical illness, who had developed flaccid weakness of extremities and could not be weaned from the ventilator as their critical illness stabilized. They characterized it as axonal motor and sensory neuropathy and distinguished it from acute neuropathy of Guillain-Barré syndrome. About that time, acute quadriplegic myopathy was also reported in ICU patients, especially those with status asthmaticus who had received neuromuscular junction blocking agents and corticosteroids. Experience from various centers all over the world in the last 2 decades has established neuromuscular weakness as an important complication of critical illness in the ICU. Three relatively distinct syndromes (critical illness polyneuropathy [CIP], critical illness myopathy [CIM], and prolonged neuromuscular blockade) have been recognized.

Recent literature has substantially contributed to our understanding of the pathophysiology and risk factors of these syndromes, but it has also generated controversy regarding the relative incidence, causative mechanisms, nosological description, and mode and extent of clinical investigations. Clinically, the difficulties stem from the fact that examination of ICU patients is often unreliable, laboratory findings of the ICU-related syndromes may overlap, and different syndromes may coexist in the same patient. Despite these limitations, the aim of clinical assessment of an ICU patient with generalized weakness is to distinguish critical illness related complications from other neurological causes, and to define the specific nature of neuromuscular weakness due to critical illness.

Understanding the Causes of Weakness in ICU Patients

Causes of generalized weakness in the ICU setting may be considered in the context of (1) pre-existing versus new-onset weakness, and (2) localization of the disease

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process within the nervous system. Various pre-existing neurological disorders, such as Guillain-Barré syndrome, myasthenia gravis, ALS, spinal cord injury, and myopathies that lead to ICU admission are well known.\textsuperscript{2,26–28} New onset generalized extremity and/or respiratory muscle weakness may be further divided into previously undiagnosed/newly acquired neurological disorders, and critical illness related disorders. Some examples of neurological disorders that may occur after admission to ICU are Guillain-Barré syndrome following infective illness or surgery, spinal cord infarct after aortic surgery, and muscle weakness due to severe electrolyte disorder.

In addition, certain disorders may be unmasked (eg, myasthenia gravis) or precipitated (eg, rhabdomyolysis) by infection or medications used in the ICU.\textsuperscript{28–30} Finally, patients with rapidly progressive weakness and respiratory compromise (Guillain-Barré syndrome, acute transverse myelitis) may get admitted to ICU before there is enough time to establish the diagnosis, or patients with unusual presentation of isolated/predominant respiratory muscle weakness (ALS, myotonic muscular dystrophy) may remain unrecognized for a considerable time after admission to the ICU.\textsuperscript{26–28}

However, neuromuscular disorders as a consequence of critical illness are now recognized as the most important cause of newly acquired weakness in the ICU. Occurrence of CIP, CIM, or a combination of the two is reported in 30–50% of patients with critical illness. A study of 92 patients with neuromuscular weakness in an ICU reported CIM in 42%, CIP in 12%, demyelinating neuropathy in 13%, motor neuron disease in 7%, neuromuscular junction disorders in 3%, and other neuropathies in 13% of those patients.\textsuperscript{31}

Another approach, which is very relevant to clinical assessment, is to classify the causes of weakness in an ICU patient according to central (intracranial) nervous system, spinal cord, and peripheral (neuromuscular) lesions. Neuromuscular disorders are, in turn, best understood as affecting different parts of the motor unit. By definition, the motor unit consists of the anterior horn cell body, its axon, terminal nerve endings, and the number of muscle fibers that it innervates.\textsuperscript{32} It is helpful to divide neuromuscular disorders based on involvement of components of the motor unit: the anterior horn cell, peripheral nerve, neuromuscular junction, and muscle. Table 1 summarizes the pre-existing and new onset causes of weakness in relation to site of involvement. The neuromuscular complications of critical illness, as noted, also affect all the components of the motor unit.

### Clinical Assessment

Onset of weakness in ICU patients may not be appreciated in the presence of severe underlying systemic ill-

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### Table 1. Classification of Neurological Causes of Motor Weakness in Intensive Care Unit Patients

<table>
<thead>
<tr>
<th>Localization</th>
<th>Pre-existing</th>
<th>Previously Undiagnosed/New-Onset</th>
<th>Critical Illness Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord</td>
<td>Trauma</td>
<td>Acute ischemia</td>
<td>Not described</td>
</tr>
<tr>
<td></td>
<td>Infarction</td>
<td>Epidural abscess</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transverse myelitis</td>
<td>Acute transverse myelitis</td>
<td></td>
</tr>
<tr>
<td>Anterior horn cell</td>
<td>Amyotrophic lateral sclerosis</td>
<td>Amyotrophic lateral sclerosis</td>
<td>Hopkins syndrome</td>
</tr>
<tr>
<td></td>
<td>Poliomyelitis (West Nile virus)</td>
<td>(predominant diaphragm weakness)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transverse myelitis</td>
<td>West Nile virus poliomyelitis</td>
<td></td>
</tr>
<tr>
<td>Peripheral nerve</td>
<td>Guillain-Barré syndrome</td>
<td>Incidental Guillain-Barré syndrome</td>
<td>Critical illness polyneuropathy</td>
</tr>
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ness, sedation, and encephalopathy. It is often brought to attention because of flaccidity and wasting of extremities or difficulty in weaning the patient from mechanical ventilation. Evaluation of such a patient requires a systematic approach and consideration of special aspects of the ICU environment.

Limitations of Neurological Examination in the ICU

It is often difficult to elicit patients’ cooperation because of inability to communicate, poor attention, sedation, and fatigability. Muscle strength testing may be inadequate and sensory examination not reliable. Acute motor deficits due to central nervous system (upper motor neuron) injury may cause hypotonia and hyporeflexia similar to lower motor-neuron lesions, and clinical differentiation between central and peripheral causes becomes difficult.33 Also, neuromuscular and central nervous system (CNS) involvement may be coincidental. Knowledge of clinical background or setting in which the weakness evolves is an important guide to differential diagnosis.

Clinical Setting of Motor Weakness

Preceding or underlying illness and its treatment in the ICU may have bearing on the nature of motor weakness. CIP often follows sepsis, systemic inflammatory response syndrome, and multiorgan failure,5,9,34 whereas CIM often occurs in the setting of treatment with intravenous corticosteroids and nondepolarizing neuromuscular blocking agents.7,16,35,36 Patients with asthma, pneumonia, organ transplant, and renal failure seem to be predisposed to development of CIM.35,36 Guillain-Barré syndrome may follow an antecedent infective illness, surgery, or trauma for which the patient may have been initially admitted to the ICU.3 Neuromuscular blocking agents and aminoglycosides may unmask latent myasthenia gravis. Similarly, drugs, infection, or trauma may precipitate rhabdomyolysis.30,38 The list of medications received by the patient in the ICU should always be checked (Table 2).

Neurological Examination

Central Nervous System Lesions

It is useful to proceed systematically to exclude CNS (intracranial) causes of weakness. These may coexist with neuromuscular disorders or be solely responsible for neurological impairment. Three major features point toward CNS involvement: asymmetric neurologic signs (right or left cerebral hemisphere), altered mental status (encephalopathy), and cranial nerve palsies (brain stem). Appropriate imaging (computed tomography, magnetic resonance imaging) and electroencephalogram usually provide the diagnosis. Important CNS processes to be considered for generalized weakness are brain stem infarct, hemorrhage, or central pontine myelinolysis, which may result in “locked-in” syndrome. Various neuromuscular disorders with generalized extremity, bulbar, and ocular involvement (eg, Guillain-Barré syndrome, myasthenia gravis, and botulism) can also mimic “locked-in” syndrome, and should be considered in the differential diagnosis if neuroimaging studies are negative. Rarely, patients with fulminant Guillain-Barré syndrome have had complete motor and sensory paralysis and absent brain stem reflexes, giving the appearance of brain death. In such patients with suspected brain death, when no cause of brain stem syndrome was detected, further investigation showed normal electroencephalogram, presence of visual evoked potentials, or preserved oculocardiac response, which refuted the diagnosis of brain death.39,40 CSF and electromyography studies led to diagnosis of Guillain-Barré syndrome, and some of these patients were successfully treated.

Spinal Cord Lesions

History of trauma in a patient with quadriplegia or paraplegia strongly favors traumatic spinal cord injury. However, many spinal cord lesions, such as acute transverse myelitis, epidural abscess, and spinal cord infarct, may present as pre-existing or new onset causes of generalized weakness in ICU patients. In the presence of flaccid weakness due to spinal shock, upper versus lower motor neuron paralysis cannot be distinguished. Presence of sensory level
on trunk, Babinski sign, flexor spasms, loss of anal reflex, loss of sphincter control, and arms weaker than legs are some useful signs of spinal cord involvement. Any suspicion of a spinal cord lesion should lead to radiologic investigation. Magnetic resonance imaging of the spine is the most useful procedure.

Neuromuscular Disorders

The main clinical features of neuromuscular diseases are weakness and wasting of extremities, hypotonia, and hyperreflexia/hyporeflexia, with or without respiratory and/or cranial musculature involvement. It is customary to localize neuromuscular disorders to different parts of the motor unit (ie, anterior horn cell, peripheral nerve, neuromuscular junction, or skeletal muscle). Diseases of the anterior horn cell, neuromuscular junction, and muscle produce pure motor syndromes, whereas most peripheral nerve disorders have sensory and motor findings. Clinical distinction among these categories may be obscured in the ICU setting because of difficulty in eliciting signs, overlapping features, and simultaneous occurrence of more than one syndrome.

Some helpful clinical signs are asymmetric weakness and fasciculations (ALS, viral poliomyelitis); paresthesia, sensory deficits, and distal symmetric weakness (peripheral neuropathy); cranial nerve palsies and dysautonomia (Guillain-Barre syndrome); and combination of ptosis and weakness of eye closure (myasthenia gravis, prolonged neuromuscular junction blockade). Further investigation with biochemical studies, nerve conduction and needle electromyography (EMG), and muscle biopsy are often necessary to arrive at a definitive diagnosis.

Laboratory Evaluation

Serum creatine kinase is elevated in primary muscle disease. The highest levels (≥10,000 international units) are seen with acute necrotizing myopathy, acute polymyositis, and rhabdomyolysis. In CIM, creatine kinase may be 10–100-fold higher than normal, peak early in illness (around 3–4 days), and tend to normalize beyond 10 days. Of note, creatine kinase may be elevated following trauma to muscle or after needle EMG examination. The investigations are tailored to the clinical differential diagnosis; for example, serum electrolytes for hypocalcemia, hypophosphatemia, and hypermagnesemia; immunological studies for vasculitides; and human immunodeficiency virus antibody testing and cerebrospinal fluid (CSF) examination for Guillain-Barré syndrome.

Electrophysiological Studies

Ever since the initial description of CIP, standard EMG and nerve conduction techniques have been employed widely to identify and classify neuromuscular disorders in the ICU setting. Some studies specifically analyzed the data on ICU patients referred for electrophysiological investigations, whereas others prospectively evaluated the pattern of electrophysiological abnormality. Experience in the last 2 decades has established the role of EMG and nerve conduction study (1) to confirm the presence of neuromuscular disorder, (2) to distinguish between primary muscle, nerve, and neuromuscular junction involvement, thus narrowing the differential diagnosis, and (3) at times, to arrive at a specific diagnosis for the given clinical picture. At the same time, methodological difficulties in the ICU, complexity of interpretation of findings, and patient discomfort pose considerable challenges. The technical aspects and basis of interpretation of conventional nerve conduction and needle EMG, and other special techniques relevant to the ICU setting, are discussed.

Conventional Motor and Sensory Nerve Conduction

These techniques are standard, reproducible, and widely used. Percutaneous stimulation and surface recording electrodes are employed. Motor response is elicited by supramaximal electrical stimulation of an extremity nerve, with recording from an appropriate distal muscle innervated by that nerve (Fig. 1). The compound muscle action potential (CMAP) is the summed response of all stimulated muscle fibers within that muscle. Stimulation at 2
points along the nerve is required to calculate motor nerve conduction velocity in that segment. Distal motor latency alone cannot be used to calculate motor conduction velocity, because it incorporates the delay at the neuromuscular junction. Sensory or mixed nerve action potential is obtained by supramaximal stimulation of a sensory or mixed nerve, with recording electrodes placed along the same nerve, usually 8–14 cm distal or proximal to the stimulating electrode. The distal motor and sensory latencies, motor and sensory conduction velocity, amplitude (onset to negative peak) of CMAP and nerve action potential, and waveforms of these potentials are noted. Abnormality of motor and sensory nerve conduction strongly favors a neuropathic process. In axonal neuropathy, CMAP and nerve action potential amplitude is reduced (corresponding to loss of axons), with normal conduction velocity in surviving axons. Demyelinating neuropathy is characterized by marked slowing of conduction and/or presence of conduction block indicated by > 50% reduced CMAP amplitude on proximal stimulation of a motor nerve, compared to that on distal stimulation (Fig. 2).

**F Wave.** Supramaximal stimulation of a motor nerve (eg, median or ulnar nerve at wrist, or peroneal or tibial nerve at ankle) produces an orthodromic volley of impulse distally to the muscle, as well as an antidromic volley that travels proximally along motor axons to the anterior horn cells. A proportion of the anterior horn cells then fire back, and the impulse travels down again to the muscle and is recorded as a late motor response, which is termed an “F wave” (Fig. 3). This represents conduction along the length of the motor nerve, including the proximal segment. In generalized neuropathy, marked slowing or absence of the F wave with relatively normal CMAP is compatible with demyelination. The F wave may be absent or lack persistence if CMAP is markedly reduced due to other causes (eg, motor neuron disease, axonal neuropathy, or advanced myopathy). The F wave is also inhibited in acute CNS lesions, as well as in sedated or unconscious patients.
Needle EMG

Needle EMG is performed with a monopolar or a concentric bipolar needle electrode, in judiciously selected muscles, based on clinical and nerve conduction findings. The standard procedure involves 3 steps (Fig. 4):

1. Spontaneous and insertion activity. Needle electrode insertion into a normal muscle at rest elicits a brief burst of insertion activity but no spontaneous activity other than end-plate noise or spikes if the needle is close to the motor end-plate region. Presence of fibrillation potentials and positive sharp waves indicates denervation or muscle necrosis separating the muscle fibers from their end-plate zone. Fasciculation potentials are seen in anterior horn cell or peripheral nerve disease. Certain abnormalities (eg, myotonic discharges) may provide specific diagnosis.

2. Steady mild voluntary contraction. With slight voluntary activation of the muscle, low threshold, semi-rhythmically firing motor unit potentials (MUPs) are recorded. The duration, amplitude, and number of phases of the MUPs are assessed. In neuropathic lesions with axonal loss, reinnervation of denervated muscle fibers through collateral sprouting of surviving axons results in large polyphasic MUPs. On the other hand, myopathic processes are associated with a reduced number of functional muscle fibers within each motor unit, and therefore MUPs are of small duration and low amplitude. Myopathic MUPs also show marked polyphasia due to decreased synchronization of muscle fiber action potentials within the motor unit.

3. Increasing/maximum voluntary contraction. Increasing the force of voluntary contraction increases the firing rate of initial MUPs and produces systematic recruitment of additional MUPs. Normally, a large number of overlapping MUPs are recorded at maximum effort, which

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<th>Muscle Contraction</th>
<th>EMG Activity</th>
<th>Normal</th>
<th>Neurogenic</th>
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<tr>
<td>I. None</td>
<td>SA</td>
<td>None</td>
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<td>II. Mild/Steady</td>
<td>MUP</td>
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<td>III. Increasing/Full</td>
<td>Recr/IP</td>
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Fig. 4. Needle electromyography (EMG). There are 3 steps to the procedure, and these waveforms show typical EMG patterns. The neurogenic pattern shows the presence of spontaneous activity, large polyphasic motor-unit potentials (MUPs), and a reduced interference pattern. The myopathic pattern shows variable spontaneous activity, small polyphasic MUPs, and a low-amplitude, full interference pattern. SA = spontaneous activity. Recr = recruitment. IP = interference pattern.

Fig. 5. Repetitive nerve stimulation at a low stimulation rate (2 Hz) in a patient with prolonged neuromuscular junction blockade. A: Decrement response that suggests neuromuscular transmission defect. B: Normal repetitive nerve stimulation response on recovery. (From Reference 26, with permission.)
creates what is called an interference pattern. Loss of functional motor units with axonal injury or conduction block produces an incomplete or reduced recruitment/interference pattern. Myopathic diseases have the normal complement of motor units but reduced numbers of functional muscle fibers, which causes a normal interference pattern with reduced amplitude. Recruitment of a large number of MUPs with weak voluntary force (early recruitment) is characteristic of a myopathic pattern.46,55

**Neuromuscular Junction Testing**

**Repetitive Nerve Stimulation.** With an electrode setup similar to that used for motor nerve conduction, a train of 10 supramaximal stimuli at 2–3 Hz is applied. A ≥ 10% decrement of CMAP amplitude from first to fourth response is considered significant and indicates compromise of neuromuscular transmission (eg, in myasthenia gravis and neuromuscular junction blockade) (Fig. 5).20,46,59 Presynaptic neuromuscular junction disorders (eg, Lambert-Eaton syndrome and botulism) have low baseline CMAP amplitude. An increment response of > 100% can be elicited following a 10-second exercise of muscle being tested or with fast (20–50 Hz) repetitive stimulation (Fig. 6).60

**Single-Fiber EMG.** The basis of single-fiber EMG is to record a pair of muscle fiber action potentials belonging to the same motor unit. Variability in the interspike interval (termed “jitter”) and absence (blocking) of second potential is observed (Fig. 7). Prolonged jitter and/or blocking characterizes neuromuscular junction dysfunction.61,62 Single-fiber EMG is more sensitive than repetitive nerve stimulation; however, it is technically demanding and requires special expertise. The procedure can be modified to stimulated single-fiber EMG for patients unable to perform voluntary contraction.63

**Train-of-4 Stimulation.** Train-of-4 stimulation is a simple bedside procedure, physiologically similar to repetitive nerve stimulation, and is used to monitor nondepolarizing neuromuscular blockade. Typically, the ulnar nerve is stimulated at the wrist (4 impulses at 2 Hz). The patient’s thumb is gently supported in abducted position, and adduction twitch, due to contraction of the adductor pollicis muscle, can be felt.64 Normally, all 4 responses are elicited and the nondepolarizing neuromuscular blockade dose is titrated to produce 1 or 2 twitches. Absence of twitches indicates complete blockade (nondepolarizing neuromuscular blockade overdose).65 However, whether train-of-4 monitoring has a definitive role in improving recovery time from neuromuscular blockade is controversial.66

**Respiratory EMG**

**Phrenic Nerve Conduction.** The phrenic nerve conduction study is particularly relevant in patients with suspected respiratory muscle weakness and those who have
difficulty weaning from the ventilator. Percutaneous stimulation of the phrenic nerves is performed bilaterally in the supraclavicular fossa, unless precluded by a central line on one or the other side of the neck (Fig. 8). Diaphragm CMAP is recorded with surface disk electrodes placed 16 cm apart, at the xiphoid process and the costal margin. Latency to onset and amplitude of CMAP are noted. Reduced diaphragm CMAP amplitude with near normal phrenic motor latency has been observed in CIP. Demyelinating neuropathies (eg, Guillain-Barré syndrome) show markedly prolonged latency and/or reduced amplitude and temporal dispersion of CMAP. A unilateral abnormality often suggests a traumatic or postoperative lesion of the phrenic nerve. Needle EMG of the Diaphragm. The needle electrode is inserted through any intercostal space, just above the costal margin, between the anterior axillary and medial clavicular lines. Diaphragm activity is identified in the form of bursts of MUPs during inspiration. Spontaneous activity can be assessed during quiet intervals between the bursts. To evaluate EMG activity of voluntary respiration, intermittent mandatory ventilation is temporarily discontinued under close supervision. Spinal cord (C3-C5) lesions, phrenic nerve injury, and CIP are associated with findings of active denervation. Severe chronic obstructive pulmonary disease, ileus, and bleeding diathesis are contraindications for needle EMG of the diaphragm.

Special Techniques

Blink Reflex. Blink reflex may be considered the electrical correlate of the corneal reflex, with the ipsilateral trigeminal nerve as the afferent limb and the bilateral facial nerve as the efferent limb of the reflex arc. Blink reflex has been used in evaluation of peripheral and central lesions of those nerves. Electrical stimulation of the supraorbital nerve elicits a direct (R1) ipsilateral response and a delayed (R2) bilateral simultaneous response from the orbicularis oculi muscles. Application of the blink reflex in ICU patients with neuromuscular disorders is based on the experience that blink reflex is abnormal in acquired demyelinating neuropathies (eg, Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy) and is unaffected in axonal neuropathies, and thus may help distinguish between Guillain-Barré syndrome and CIP.

Direct Muscle Stimulation. Rich et al initially applied the technique of direct muscle stimulation in ICU patients, and they found inexcitability of muscle in patients with acute quadriplegic myopathy. Direct muscle stimulation is performed by placing both stimulating and recording needle electrodes in the muscle distal to the end-plate zone (Fig. 9). A direct muscle-stimulated CMAP is recorded, and then the motor nerve of the muscle is stimulated to obtain a nerve stimulated CMAP with the same recording electrode. In neuropathic lesions (eg, CIP), nerve stimulated CMAP may be reduced or absent, but direct muscle-stimulated CMAP is normal. In contrast, CIM is associated with reduced or absent CMAP on nerve stimulation, as well as on direct muscle stimulation. This observation formed the basis for investigating direct muscle stimulation to distinguish between CIP and CIM. Later studies used the ratio of the nerve-stimulated CMAP to the direct muscle-stimulated CMAP, or the absolute amplitude of the direct muscle-stimulated CMAP, to determine muscle membrane excitability. Rich and Pinter also studied an experimental model of acute quadriplegic myopathy and found that inexcitability of muscle membrane was related to inactivation of sarcolemma Na^+ channels. The technique has provided a diagnostic method and helped to
understand the pathophysiology of CIM. The procedure, however, is technically demanding and has been used only in a few centers so far.

Muscle and Nerve Biopsy

Nerve and muscle histological studies have substantially contributed to our understanding of the wide clinicopathological spectrum of new onset weakness in critically ill patients. Various studies on nerve histology (autopsy or surgical pathology) in patients with CIP have confirmed axonal degeneration of motor and sensory nerve fibers without inflammation. Through muscle biopsy studies it became obvious that CIM, as an isolated syndrome or in combination with CIP, may be more common than the neuropathic syndrome. Experience with muscle biopsy has led to definition of various histological subtypes (eg, acute necrotizing myopathy, thick myosin filament loss myopathy [Fig. 10], and type II fiber atrophy). Many patients have various combinations of these changes. Generally, the role of muscle biopsy in a weak ICU patient is 2-fold: (1) to distinguish a neuropathic from a myogenic process, and (2) to determine the specific etiology, based on morphologic characteristics (eg, polymyositis/dermatomyositis, mitochondrial myopathy, or CIM). Percutaneous punch muscle biopsy or open muscle biopsy can be performed, and the interpretation should be done by experienced individuals. Therefore, the procedure is often carried out for research purposes or when an underlying neuromuscular disorder is suspected because of an absence of risk factors for CIM or lack of improvement in 3–4 weeks. Nerve biopsy is not indicated in clinical investigations of these patients, unless a specific disorder, such as vasculitic neuropathy, is suspected.

Disorders That Cause Neuropathic Weakness

Critical Illness Polyneuropathy

CIP has a rather stereotypical evolution in the ICU. Initial critical illness (eg, sepsis, burn, trauma) is followed by multiorgan failure, septic encephalopathy, difficulty weaning from the ventilator in the absence of cardiopulmonary compromise, and generalized muscle weakness. Weakness is indicated by the patient’s inability to move extremities in response to pain, while strong facial grimacing shows wakeful status. The degree of weakness ranges from moderate paresis with hyporeflexia to severe areflexic quadriplegia. The weakness is predominant distally and in the lower extremities. The cranial nerves are spared, although facial weakness is occasionally reported. Sensory impairment occurs in only 50% of patients, and this may reflect difficulty in performing sensory examination in the ICU. Hyporeflexia/areflexia is common, although muscle stretch reflexes may be normal in about one third of the patients, and at times may be exaggerated if there is concomitant CNS involvement.
EMG and nerve-conduction studies show low amplitude of CMAP and nerve action potential, with near normal conduction velocity and the presence of fibrillation and positive sharp wave potentials consistent with axonopathy.\(^2\,6\,12\,19\,34\,42\,69\) Abnormal phrenic nerve conduction (bilateral reduced or absent diaphragm CMAP) is reported in about 50–80% of patients.\(^19\,82\) Clinical CIP may occur in 30–50% of ICU patients, but prospective electrophysiological studies describe an incidence of 70–80%.\(^24\,69\,82\) The occurrence of CIP correlates with duration of ICU stay and severity of sepsis. High mortality (60%) in patients with CIP probably relates to underlying critical illness, but some investigators think that mortality is higher in patients with CIP than in those with comparable Acute Physiology and Chronic Health Evaluation (APACHE III) score without CIP.\(^83\) Follow-up studies showed severe paralysis in 4 of 15 survivors, and impaired quality of life in 11 of 13 survivors. Long-term outcome with moderate-to-severe deficits is variably reported in 30–80% of cases and appears to be much less favorable than Guillain-Barré syndrome or CIM.\(^13\,84\) Clinical and laboratory features that distinguish among these syndromes are outlined in Table 3.

Guillain-Barré Syndrome

Guillain-Barré syndrome is the most common neuromuscular disorder that requires admission to the ICU, as well as the most important differential diagnosis for CIP. Antecedent illness, rapid ascending flaccid paralysis, and

| Findings |
|-------------------|-----------------|-------------------|
| **Critical Illness Polyneuropathy** | **Guillain-Barré Syndrome** | **Critical Illness Myopathy** |
| **Clinical setting** | Sepsis | Antecedent viral | Neuromuscular blocking drugs |
| | Multiorgan failure | Surgery | Corticosteroids |
| | Septic encephalopathy | Campylobacter jejuni | Asthma |
| | | HIV | Organ transplant |
| **Motor weakness** | Generalized or distal predominant | Generalized, ascending, areflexia | Generalized or proximal predominant |
| **Cranial nerve palsy** | Rare | Common | Occasional |
| | | Unilateral/bilateral facial Bulbar | Ophthalmoparesis, bilateral facial |
| **Dysautonomia** | No | Yes | No |
| **Sensory deficit** | Distal | Mild, distal | No |
| **Creatine kinase** | Normal | Normal | Elevated |
| **Nerve conduction** | Reduced CMAP and SNAP amplitude | Marked slowing, conduction block | Reduced CMAP amplitude |
| | | | Normal SNAP amplitude |
| **Needle EMG** | Abnormal spontaneous activity common | Abnormal spontaneous activity may be seen | Mild or no abnormal spontaneous activity (pronounced in necrotizing) |
| | Reduced recruitment | Reduced recruitment | Small polyphasic MUPs; early recruitment |
| | Large, polyphasic MUPs | Normal MUPs initially; may be large, polyphasic MUPs later | |
| **Direct muscle stimulation** | Normal | Normal | Absent or reduced |
| **Muscle biopsy** | Neuropathic changes | Neuropathic changes | Myopathic |
| | | | Thick myosin filament loss |

HIV = human immunodeficiency virus
CMAP = compound muscle action potential
SNAP = sensory nerve action potential
EMG = electromyography
MUP = motor unit potential
cranial nerve involvement are characteristic features. Elevated CSF protein and electrodiagnostic findings of markedly slow nerve conduction, prolonged or absent F waves, and conduction block (which suggest demyelinating neuropathy) clearly distinguish it from CIP.6,33,50 The presence of dysautonomia, abnormal blink reflex, and prolonged phrenic nerve latency are also helpful.50,71,75 The axonal variant of Guillain-Barré syndrome (about 5% of cases) may be difficult electrophysiologically to differentiate from CIP. This variant is reported most often in association with Campylobacter jejuni infection and GM1 ganglioside antibody.25 In general, testing for ganglioside antibody levels is not indicated. It is important to distinguish incidental Guillain-Barré syndrome in the ICU (which may follow a medical illness or surgery) from CIP, because specific treatment with intravenous immunoglobulin or plasmapheresis is indicated for Guillain-Barré syndrome.

Other Acute Neuropathies

Occasionally, acute neuropathies due to uncommon causes have been encountered in the ICU setting. Human immunodeficiency virus infection is associated with various clinical forms of peripheral neuropathy and may also present with acute polyneuropathy similar to Guillain-Barré syndrome.38 In the presence of risk factors, human immunodeficiency virus antibody testing is relevant. Rarely, neuropathy of acute intermittent porphyria may develop in the ICU, because acute attack can be precipitated by medications or infection. It is an acute axonal neuropathy, CSF protein is not elevated, and features such as seizures, arrhythmia, abdominal pain, and psychiatric symptoms may be associated.28,38 Toxic neuropathies are unlikely to be encountered in the ICU. Some possibilities are prior cancer chemotherapy (platinum, taxanes, vinca alkaloids, suramin), amiodarone, and metronidazole.38 Peripheral nerve involvement in vasculitis usually presents as subacute onset of mononeuritis multiplex. Widespread involvement may mimic symmetric or asymmetric polyneuropathy.85 Involvement of other organs and findings of multifocal axonal neuropathy on EMG are suggestive of the diagnosis. Suspicion of vasculitic neuropathy is an important indication for nerve biopsy.

Compression Neuropathies

ICU patients may be prone to development of focal neuropathies at compression sites (eg, ulnar nerve at elbow, peroneal nerve at fibular head, and radial nerve in spiral groove), due to positioning, weight loss, et cetera. Multiple bilateral focal compressive syndromes may mimic distal polyneuropathy. On electrophysiologic testing, focal slowing of nerve conduction and/or conduction block at common sites of compression, and neurogenic EMG pattern in corresponding muscles, are diagnostic.45,47 Compression neuropathies superimposed on CIP have been reported to contribute to long-term deficits.86

Acute Poliomyelitis

Poliomyelitis due to poliovirus is no longer prevalent; however, similar acute paralysis may occur due to non-poliovirus infection. Acute, flaccid, and often asymmetric paralysis due to West Nile virus is being increasingly recognized.87 Bulbar and respiratory muscles may also be involved. Patients may be admitted to the ICU for altered mental status due to West Nile virus encephalitis or meningitis and later develop flaccid paralysis. Predominantly proximal, asymmetric weakness, preserved reflexes, and normal sensation distinguish West Nile virus paralysis from Guillain-Barré syndrome and CIP. CSF shows increased protein level and lymphocytic pleocytosis, and immunoglobulin M antibody to West Nile virus is detected in serum or CSF. Electrodiagnostic studies show reduced CMAP with normal motor nerve conduction velocity, normal sensory responses, and neurogenic EMG in segmental pattern. Rarely, West Nile virus has been associated with demyelinating neuropathy similar to Guillain-Barré syndrome.88

Amyotrophic Lateral Sclerosis

Previously undiagnosed patients with ALS may present with acute ventilatory failure due to isolated or predominant respiratory muscle weakness.31,89 They fail to wean from the ventilator and show signs of limb wasting, generalized fasciculations, and brisk reflexes. Diagnosis is confirmed by electrodiagnostic studies, which reveal widespread active denervation, chronic reinnervation, and fasciculation potentials. Lacomis et al recognized 5 patients with ALS among 92 ICU patients referred for electrophysiological study.31

Hopkins Syndrome

In 1974, Hopkins90 reported a polio-like syndrome in children following acute asthma. About 30 patients have been reported since then.91 There is acute flaccid monoparesis or, at times, paraparesis. Marked atrophy and persistent deficits are noted on follow-up. EMG is consistent with motor neuron involvement, and muscle biopsy shows grouped atrophy. Recently, the disorder was reported in adults as well. The etiology is not known; however, increased CSF protein and lymphocytic pleocytosis, and occasional improvement after intravenous immunoglobulin therapy, may point to an immune or inflammatory process.92
Disorders That Cause Myopathic Weakness

Critical Illness Myopathy

A syndrome of acute myopathy in a patient with asthma who received neuromuscular blocking agents and corticosteroids was documented in the 1970s. Primary muscle involvement in ICU patients initially remained under-recognized, but there has been increasing interest in and multimodal investigations of ICU paralysis syndromes, which may include that CIM may be the commonest newly acquired neuromuscular disorder in the ICU. Predisposing factors are acute asthma, exacerbation of chronic obstructive pulmonary disease, organ transplant, acute respiratory distress syndrome, sepsis, and use of high doses of corticosteroids and neuromuscular-blocking agents. Patients develop symmetric diffuse weakness of all extremities, muscle wasting, hyporeflexia, and failure to wean from the ventilator. The major differential diagnosis is from CIP and, rarely, other acute myopathies (rhabdomyolysis, acute polymyositis, electrolyte disorders). The clinical setting, preserved reflexes, normal sensory examination, ophthalmoplegia, and facial weakness may favor the possibility of CIM; however, there are no definitive clinical findings to distinguish CIM from CIP, and the examination in the ICU may be unreliable.18,33,78

Elevated serum creatine kinase in acute weakness is an important diagnostic feature, especially in the early part of the illness. Typical EMG features include low amplitude, short duration and polyphasic MUPs, with good recruitment pattern despite pronounced weakness. CMAP amplitude is reduced and sensory potentials are normal. Fibrillation and positive sharp wave potentials, which are usually indicative of axonal injury, also occur in necrotizing myopathies. There are many caveats to interpreting electrophysiological studies in the ICU. Assessment of voluntary EMG may be difficult when the patient cannot activate motor units due to severe weakness, sensory potentials may be technically difficult to elicit, and reduced CMAP with normal motor nerve conduction is seen in CIP as well as CIM. It is therefore not surprising that many investigators have pointed out the difficulties in distinguishing between the 2 neuromuscular syndromes,10,21,22,25,42 The newer technique of direct muscle stimulation demonstrates muscle membrane inexcitability in CIM.20 The ratio of nerve-stimulated CMAP to direct muscle-stimulated CMAP is reduced in neuropathic lesions and is closer to 1.0 in CIM.21 Recent studies show that combining direct muscle stimulation with routine studies is useful in proper classification of neuromuscular weakness in the ICU; however, the technique is not routinely applicable as yet.22,76

Muscle biopsy shows varying severity of myopathic changes, in contrast to grouped atrophy in neuropathy, but, being an invasive procedure, it is not routinely employed for clinical diagnosis. Histopathological studies show varying degrees of muscle fiber necrosis, most prominently in acute necrotizing myopathy, without inflammatory cells. Thick myosin filament loss is a distinctive abnormality in CIM (see Fig. 10). Predominant type II muscle fiber atrophy has been termed cachectic myopathy.78 Stibler et al noted decreased myosin/actin ratio in percutaneously obtained muscle biopsies of CIM patients, and suggested that it may be useful for rapid diagnosis. For clinical purposes, the combination of predisposing events, clinical findings, and electrophysiological investigation allows a reasonable diagnosis of CIP or CIM (see Table 3). Muscle biopsy is considered if other causes of myopathy (eg, polymyositis) are suspected. Most of the advanced techniques are relevant for research purposes.

Rhabdomyolysis

Trauma, sepsis, and various medications (see Table 2) can precipitate acute rhabdomyolysis in ICU patients. Muscle pain, swelling, predominant proximal or generalized weakness, and markedly raised serum creatine kinase are noted. Myoglobinuria, acute renal failure, and other systemic complications are present.28,43

Other Causes of Myopathy

Several primary muscle diseases may present with initial manifestations of respiratory compromise (eg, polymyositis, mitochondrial myopathy, and acid maltase deficiency). Patients with myotonic muscular dystrophy or congenital myopathies may decompensate after general anesthesia. Such patients are emergently admitted to ICU, and the underlying muscle disease may be suspected and evaluated only later during the ICU stay.38,94 Muscle biopsy is diagnostic and needs to be considered if a patient in whom CIM is suspected does not show improvement over a few weeks.

Disorders of Neuromuscular Transmission

Prolonged Neuromuscular Junction Blockade

Patients treated with high doses of nondepolarizing neuromuscular blocking agents such as vecuronium and pancuronium may have persistent weakness and fail weaning from the ventilator, even after the blocking drugs have been discontinued.14,15 This prolonged blockade may last from several hours to weeks. Patients with renal failure, hepatic dysfunction, acidosis, or hypermagnesemia are more prone to this complication. Examination shows generalized weakness, normal or reduced reflexes, and normal sensation. Bilateral ptosis, and facial and jaw muscle weakness may be present.26,33 Electrophysiologic features are...
reduced CMAP amplitude and decrementing response on 2–3 Hz repetitive nerve stimulation. The physiologic abnormality reverses on clinical recovery.26,38 Patients with uncomplicated prolonged neuromuscular blockade recover completely, usually in 1–2 weeks. The condition may coexist with CIP or CIM and has been reported to progress to CIM on sequential studies. Recognition of prolonged neuromuscular blockade has led to more judicious use of neuromuscular blocking drugs in the ICU.65

Myasthenia Gravis

Patients with myasthenia gravis typically require admission to the ICU for myasthenic crisis or cholinergic crisis. Several factors, such as infection, electrolyte disorder and drugs used in the ICU (see Table 2), may unmask latent myasthenia gravis. Rarely, respiratory failure may be the presenting feature in myasthenia gravis. Clinically, ptosis, ophthalmoparesis, and facial and bulbar weakness are common, in addition to generalized weakness. Diagnosis is based on positive edrophonium test, decrementing response on repetitive nerve stimulation, and presence of serum acetylcholine receptor antibody. Abnormal jitter on single-fiber EMG is a very sensitive diagnostic test, but is not routinely employed. Between 85% and 90% of patients with generalized myasthenia gravis are seropositive for acetylcholine receptor antibody. Among the seronegative patients, a subgroup with antibody to muscle-specific tyrosine kinase has been identified.95 These patients with myasthenia gravis have certain atypical features, including prominent neck extensor, facial and respiratory muscle weakness, and poor response to acetylcholine-esterase inhibitors. Respiratory crisis may be a presenting feature, so in a patient with suspected generalized myasthenia gravis who is seronegative for acetylcholine receptor antibody, serum assay for muscle-specific tyrosine kinase antibody should be considered.

Other Neuromuscular Junction Disorders

Lambert-Eaton Syndrome. This is a presynaptic neuromuscular transmission disorder due to calcium channel antibodies, which impair acetylcholine release from the nerve terminal. It is usually associated with small-cell lung cancer but may also occur as an idiopathic autoimmune disorder. Reduced CMAP on nerve conduction and incrementing response on high frequency repetitive nerve stimulation are characteristic. Similar to myasthenia gravis, patients with Lambert-Eaton syndrome may also present with previously unrecognized or unmasked weakness in the ICU.28,29

Botulism. Generalized weakness and cranial nerve involvement in botulism may resemble Guillain-Barré syndrome, but paralysis is often described as descending, and deep tendon reflexes may be preserved.38 Blurred vision and dilated pupils due to paralysis of accommodation are noted. This is also a presynaptic disorder, and electrophysiologic findings of reduced CMAP and increment on tetanic stimulation are observed.

Summary

Complications of critical illness, including CIP, CIM, and prolonged neuromuscular blockade, are now regarded as the major cause of new onset weakness in the ICU setting. These need to be distinguished from other neurological disorders that may begin after admission to the ICU, or when a diagnosis has not been established prior to an emergency admission. The first step in clinical examination is to distinguish CNS lesions, especially brain stem and spinal cord lesions, and to obtain magnetic resonance imaging or computed tomography of the brain or spine, if indicated. Special attention should be paid to patients with “locked-in” syndrome, since this may result from structural brain stem lesions or neuromuscular disorders. Neurological examination in the ICU can be challenging; however, combined clinical and electrophysiological assessment helps delineate anterior horn cell, nerve, muscle, and neuromuscular junction disorders. The nature of the underlying illness and the drugs received in the ICU should be noted. Some of the neurological causes to be considered are new onset Guillain-Barré syndrome, latent myasthenia gravis, predominant respiratory involvement in ALS, rhabdomyolysis, flaccid paralysis associated with West Nile virus, and muscle-specific tyrosine kinase antibody myasthenia gravis presenting with respiratory crisis.

Typical features of CIP include evidence of systemic inflammatory response syndrome and multiorgan dysfunction, followed by generalized or distal weakness, distal sensory deficits, spared cranial nerves, and findings of axonopathy on EMG. CIM often follows use of high doses of neuromuscular blocking drugs and corticosteroids. Generalized or proximal weakness, elevated creatine kinase, and myopathic pattern on EMG are noted. Severe areflexia quadriplegia, markedly elevated creatine kinase, myoglobinuria, and muscle fiber necrosis on muscle biopsy are characteristic of acute necrotizing myopathy. Thick myofibril filament loss is another distinct pathological feature of CIM. The technique of direct muscle stimulation has defined inexcitability of muscle membrane as a mechanism of weakness in CIM and has been used by some investigators to distinguish CIM from neuropathic lesions. Muscle biopsy may be used to distinguish between neuropathic versus myopathic lesions, to define type of CIM, and to establish a specific diagnosis when an underlying muscle disease is suspected.
REFERENCES


Clinical Approach to the Weak Patient in the Intensive Care Unit

Discussion

Deem: Which patients should receive muscle biopsy? How do you determine when to do a muscle biopsy?

Upinder Dhand: The main reason for muscle biopsy is to diagnose previously unsuspected underlying muscle disease or to distinguish between ICU-related syndromes. The latter may become more relevant from a research point of view—that is, understanding the relationship of various ICU factors to different neuromuscular syndromes. Most of the time, muscle biopsy is clinically indicated only in selected cases in whom an additional or previously undiagnosed primary muscle disease is suspected.

Deem: Do you use direct muscle stimulation in your hospital?

Upinder Dhand: No, I’m not using that technique. I am aware of only 2 groups doing it: Rich’s, at University of Pennsylvania,1 and Trojaborg’s, at Columbia University.2

Upinder Dhand: We’re all probably learning from experience. As Steve Deem was also saying, these may be considered as one entity. Now you may just call it a neuromuscular syndrome in the ICU setting, and some authors have used the term “critical-illness neuromyopathy.” But there is confusion for several reasons. One is that clinical examination and investigations may not clearly distinguish between critical illness neuropathy and myopathy, or the 2 syndromes may coexist. Maybe there is a whole spectrum with neuropathy at one end, myopathy at the other, and overlap in between. The reason I want to differentiate between the two is because of the outcome. The long-term care may be different.

I think critical illness neuropathy probably has more residual deficits and greater chance of mortality, whereas in critical illness myopathy the outcome is probably much better—other than patients who have fulminant, necrotizing myopathy. Moreover, investigations may help identify a different neurological cause. And, finally, I think it is particularly important for

So mainly it comes down to suspicion of critical illness polyneuropathy or myopathy. And we’ve concluded that it really doesn’t matter which one it is, because clinically you deal with them in the same way. What do you think?

Upinder Dhand: I think we all are probably learning from experience. As Steve Deem was also saying, these may be considered as one entity. Now you may just call it a neuromuscular syndrome in the ICU setting, and some authors have used the term “critical-illness neuromyopathy.” But there is confusion for several reasons. One is that clinical examination and investigations may not clearly distinguish between critical illness neuropathy and myopathy, or the 2 syndromes may coexist. Maybe there is a whole spectrum with neuropathy at one end, myopathy at the other, and overlap in between. The reason I want to differentiate between the two is because of the outcome. The long-term care may be different.

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REFERENCES


Jubran: In what clinical settings do you use needle electrodes to obtain diaphragm EMG? Do you use ultrasound to help guide the measurements? How well do patients tolerate the procedure?

Upinder Dhand: When I’m doing an EMG study in the ICU, and the question is about difficulty in weaning, I test the phrenic nerve conduction and the diaphragm with needle EMG, except when there is an obvious contraindication. For example, in a patient with severe COPD, the lung may be at a much lower level and the procedure could be risky. Or in a patient who has had laparotomy and accessing the diaphragm may be difficult. But usually it’s not difficult.

When you put the needle through the intercostal space, you first run into the intercostal muscles, and, incidentally, you can look for denervation in the intercostal muscle itself, and then go on to the diaphragm. The last portion of the diaphragm is actually directly by the thoracic cage, and the pleura is already reflected about an inch or so higher. I think ICU patients probably tolerate the procedure better than other patients, but I do it in my routine laboratory also, in patients with breathing difficulty and neuromuscular weakness. It is fairly well tolerated.

Mehta: We have a really difficult time getting EMGs. It can take months. So mainly it comes down to suspicion of critical illness polyneuropathy or myopathy. And we’ve concluded that it really doesn’t matter which one it is, because clinically you deal with them in the same way. What do you think?
people who are interested in this subject to distinguish between the two, because we are still in the process of understanding these disorders. So I still prefer to investigate.

With regard to getting the EMGs in the ICU, we have a policy that if we get a call for an in-patient EMG, it is done within 24 hours. I don’t come at night, but it is within 24 hours.

Mehta: We can’t get EEGs within 24 hours!

Hill: You cited a mortality rate of 60% for critical illness polyneuropathy, but I see it as a manifestation of multiple organ system failure, in association with the sepsis syndrome, as in ARDS [acute respiratory distress syndrome], in which mortality is 40% to 50%. But people generally don’t die of respiratory failure. Is that the case with critical illness polyneuropathy? Are people dying of multiple organ system failure rather than the neuropathy, per se?

Upinder Dhand: Yes. Various authors have mentioned that the mortality is related to the severe underlying illness, so it is not directly the result of critical illness polyneuropathy.

Deem: I’ll address that question in my upcoming talk. I have a question about train-of-4 monitoring and neuromuscular blockade in the ICU. At our institution we don’t use prolonged neuromuscular blockade nearly as much as we used to, and I don’t think we see prolonged neuromuscular blockade as a cause of weakness much any more. I’m interested to know what other people report in that regard. Personally, I don’t think train-of-4 monitoring is very useful, because it’s technically difficult, like EMG. There’s edema, and the nurses aren’t very familiar with the technique. I saw an instance where they were having problems and we discovered that the nerve stimulator’s battery was dead. I think the best way to prevent prolonged neuromuscular blockade is to not use the drugs, or to use them for short periods of time, and to stop them every day and reassess the patient.

Mehta: I have one more comment related to Herridge’s outcomes study with 100 ARDS patients. The most interesting finding was that these patients are not limited by pulmonary function at all. Their pulmonary function within 3, 6, and 12 months was essentially normal. But they’re limited by peripheral muscle weakness. And the next phase of Herridge’s research program is going to focus on preventive measures for that weakness. A major contributor may be neuromuscular blockers. We use neuromuscular blockers much less frequently than we used to. We don’t usually use daily interruption of the blockers, but that’s a really good strategy. We’re very strict about using train-of-4 monitoring, even when using short-acting agents such as cisatracurium.

REFERENCE
REVIEW ARTICLE
Fat embolism

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Summary
Fat embolism syndrome is a collection of respiratory, haematological, neurological and cutaneous symptoms and signs associated with trauma and other disparate surgical and medical conditions. The incidence of the clinical syndrome is low (< 1% in retrospective reviews) whilst the embolisation of marrow fat appears to be an almost inevitable consequence of long bone fractures. There is debate over the pathogenesis of fat embolism syndrome and it seems a variety of factors interact to produce a spectrum of end organ damage. Many therapeutic interventions and prophylactic strategies have been tried with varying success. Current treatments are supportive and the condition is usually associated with a good outcome. The literature on fat embolism syndrome is extensive and this review aims to discuss the incidence, aetiology, pathophysiology, diagnosis and treatment of fat embolism.

Keywords  Fat embolism: incidence; aetiology; pathophysiology; diagnosis; treatment.

Definition
Fat embolism describes both fat in the circulation and a clinical syndrome. As the former can occur without the latter, it is sensible to define each entity, acknowledging that there may be some overlap in clinical practice.
1 Fat embolism (FE) is fat within the circulation, which can produce embolic phenomena, with or without clinical sequelae.
2 Fat embolism syndrome (FES) is fat in the circulation associated with an identifiable clinical pattern of symptoms and signs.

Diagnosis of fat embolism syndrome
Clinical features
Fat embolism syndrome is a collection of symptoms and signs; as some of the manifestations are common to other critical illnesses, the diagnosis is often made by exclusion. The presentation may be fulminating with pulmonary and systemic embolisation of fat, right ventricular failure and cardiovascular collapse. This can occur intra-operatively [1]. More usually, the onset is gradual, with hypoxaemia, neurological symptoms, fever and a petechial rash, typically 12–36 h following injury [2]. Gurd suggested the use of ‘major’ and ‘minor’ clinical signs to make the diagnosis of FES (Table 1) [3].

The presence of any one major plus four minor criteria in addition to fat macroglobulaemia constitute FES. Using these criteria, the authors commented that it was important to examine blood daily as recent fat emboli, a change in fat quantity or a change in appearance of the globules may be associated with development of the clinical syndrome. Gurd’s criteria have been criticised for being unreliable because fat droplets can frequently be found in the blood of healthy volunteers and trauma patients without any clinical evidence of FES [4]. Lindeque suggested that Gurd’s criteria may underdiagnose the syndrome and proposed the following criteria based on respiratory parameters (Table 2) [5]. Any patient with a fractured femur and/or tibia showing one or more of these criteria was judged as having FES. These criteria lead to a diagnosis of FES in 29% of patients (in a series of 55) which is higher than other series, especially as this study excluded patients with chest injuries where some of Lindeque’s clinical signs may occur without FE.

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The most frequent presentation of FES is with respiratory symptoms and signs. Severity is variable but respiratory failure is relatively common. Bulger reported that 44% of the 27 patients diagnosed as having FES required a period of mechanical ventilation [6]. A 15-year study of trauma patients in the West Indies found 14 cases, four of whom required mechanical ventilation [7]. However, gas exchange deteriorates after long bone fractures with or without FE. In 16 of 28 patients with lower limb long bone fractures, the oxygen tension (P$_{O_2}$) was reported to be less than 7.3 kPa [5] and, similarly, in another study of patients with multiple injuries, the P$_{O_2}$ was reported to be less than 9.3 kPa in 90% of patients [8].

A petechial rash is pathognomonic of FES and in up to 60% of patients a rash may be present, usually on the conjunctiva, oral mucous membranes and skin folds of the neck and axillae. This curious distribution may be explained by fat droplets accumulating in the aortic arch prior to embolisation to nondependent skin via the subclavian and carotid vessels [9]. Factors contributing to the rash may be stasis, loss of clotting factors and platelets and endothelial damage from free fatty acids (FFAs) leading to rupture of thin-walled capillaries [10].

Neurological manifestations are also frequently seen [7, 11, 12] and signs range from drowsiness and confusion to coma. In one series, five of 14 patients were unconscious, four had decerebrate posturing and one suffered tonic-clonic seizures. Minor global dysfunction appears to be most common, but focal signs, such as hemiparesis or partial seizures, are reported. Fortunately, the severe neurological symptoms of FES frequently resolve. Central nervous system involvement has been reported in the absence of pulmonary features but with a petechial rash, fever, tachycardia and hypotension [13].

**Investigations**

A wide range of investigations have been used to identify FES. However, none of these is 100% specific and this may reflect the multisystem pathology.

Thrombocytopenia (platelet count $< 150 \times 10^9 \, \text{l}^{-1}$) and unexplained anaemia are common (37% and 67%, respectively) [6]. The mechanism causing thrombocytopenia is unclear but both platelet activation by bone marrow emboli with thrombus formation and platelet consumption due to disseminated intravascular coagulation (DIC) have been postulated [14]. Plasma FFA levels rise following trauma and this may result in hypocalcaemia due to their affinity for calcium [15]. Accompanying hypoalbuminaemia has been suggested as a predisposing factor because FFAs bind to albumin and so are rendered innocuous [16].

Blood and urinary analysis may show fat globules, although both of these are non-specific signs. The chest X-ray classically shows multiple bilateral patchy areas of consolidation typically in the middle and upper zones giving rise to a 'snow storm appearance'.

Specific biochemical tests have been suggested to aid diagnosis. Serum lipase and phospholipase A$_2$ (PLA$_2$) rise in FE related lung injury [14, 17]. However, these increases are not specific to trauma victims in whom FES occurs [18, 19] and may merely reflect altered lipid metabolism following trauma [20].

A pulmonary artery catheter has been advocated for diagnosis of fat embolism either by detecting a rise in mean pulmonary arterial blood pressure [21] or by sampling pulmonary artery blood for fat. Bronchoscopy and bronchoalveolar lavage (BAL) have been used to provide samples containing macrophages. As macrophages act as lung scavengers, they might be expected to contain fat in FES. BAL in trauma patients has been proposed as a specific method for diagnosing FES within the first 24 h [22, 23]. However, there are difficulties in obtaining satisfactory samples, as shown in one study where only 67 out of 96 samples were adequate for analysis due to low yield of macrophages [24]. Also, the stain used in these investigations is a stain for neutral fat (oil red O) which does not produce macrophages. As macrophages act as lung scavengers, they might be expected to contain fat in FES. BAL in trauma patients has been proposed as a specific method for diagnosing FES within the first 24 h [22, 23]. However, there are difficulties in obtaining satisfactory samples, as shown in one study where only 67 out of 96 samples were adequate for analysis due to low yield of macrophages [24]. Also, the stain used in these investigations is a stain for neutral fat (oil red O) which does not produce macrophages [25]. Despite these reservations, the use of a threshold value (such as 30%) of macrophages staining positive might be useful in trauma patients. Regrettably, both pulmonary artery blood aspiration and BAL samples lack the sensitivity and specificity to detect subclinical FES but the absence of macrophages staining for fat on BAL should prompt the search for alternative reasons for hypoxaemia.
Radiology may be useful where neurological involvement is suspected. Computer tomography (CT) scanning may show generalised cerebral oedema or high-density spots but in general is non-specific and unhelpful. Magnetic resonance imaging (MRI) shows greater promise as it may detect lesions in the presence of a normal CT scan. Specific changes include both low-density areas on T1-weighted images and high-density regions on T2-weighted images [26]. The distribution of involvement seen on MRI may be characteristic (cerebral deep white matter, basal ganglia, corpus callosum and cerebellar hemispheres). Suzuki noted that there were multiple spotty lesions along the boundary zones of vascular territories suggestive of fat globules blocking capillaries [27]. The radiological abnormalities resolve as the clinical signs improve and so MRI may become a useful tool for quantifying FES injury [28].

Incidence

Most large clinical series investigating FES involve elective orthopaedic or trauma surgery. The reported clinical incidence tends to be low (Table 3). These studies are striking because the incidence in retrospective long-term reviews is low (< 1%) while prospective studies state a far higher but consistent incidence (11–19%). The incidence of FE at post-mortem is several times that suspected clinically.

Incidence diagnosed by clinical criteria

In a 10-year review in an American level one trauma centre there was an incidence of FES of 0.9% using Gurd's diagnostic criteria [6]. There was no obvious correlation with severity, site or pattern of injury and FES. This contrasted with other studies which have shown an increase in incidence of FES with an increasing number of 'at-risk fractures' (a fracture involving femur, tibia or pelvis) [29, 38].

Incidence determined by physiological monitoring

When less subjective methods of evaluating the end organ effects of FE are used, the incidence rises. Using the alveolar–arterial oxygen tension difference as a marker for lung injury, one prospective study reported an incidence of 11% [12]. None of the patients had another cause for hypoxaemia other than FE and 40% of those with an increased alveolar–arterial oxygen tension difference had a petechial rash.

Incidence as identified by sophisticated imaging of emboli

Sophisticated measurement of emboli in the circulation with echocardiography has also been used to demonstrate a high incidence of embolic phenomena. In one study of 110 orthopaedic patients (111 procedures), transoesophageal echocardiography (TOE) detected embolic showers

Table 3 The incidence and mortality of fat embolism syndrome in recently reported series. TOE, transoesophageal echocardiography. FES, fat embolism syndrome

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Study design</th>
<th>Incidence (n)</th>
<th>Mortality (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulger [6]</td>
<td>1997</td>
<td>10 years review of trauma cases</td>
<td>0.9% (27)</td>
<td>7% (2)</td>
</tr>
<tr>
<td>Robert [29]</td>
<td>1993</td>
<td>25 years retrospective review</td>
<td>0.26% (20)</td>
<td>20% (4)</td>
</tr>
<tr>
<td>Fabian [12]</td>
<td>1990</td>
<td>96 consecutive long bone fractures</td>
<td>11% (10)</td>
<td>10% (1)</td>
</tr>
<tr>
<td>Kallenbach [30]</td>
<td>1987</td>
<td>Randomised trial of corticosteroids; 82 trauma patients overall</td>
<td>13% (11) overall</td>
<td>Nil</td>
</tr>
<tr>
<td>Lindeque [5]</td>
<td>1987</td>
<td>Randomised trial of corticosteroids; 55 trauma patients overall</td>
<td>13% (7) by Gurd criteria</td>
<td>Nil</td>
</tr>
<tr>
<td>Chan [8]</td>
<td>1984</td>
<td>80 consecutive trauma patients</td>
<td>13% (7) by revised criteria</td>
<td>8.75% (7)</td>
</tr>
<tr>
<td>Schonfield [31]</td>
<td>1983</td>
<td>Randomised trial of corticosteroids; 62 trauma patients overall</td>
<td>35% of multiply injured patients</td>
<td>2.5% (2)</td>
</tr>
<tr>
<td>Myers [32]</td>
<td>1977</td>
<td>100 consecutive trauma patients with long bone fractures</td>
<td>15% (9) overall</td>
<td>Nil</td>
</tr>
<tr>
<td>Christie [33]</td>
<td>1995</td>
<td>111 long bone fracture fixations</td>
<td>(No cases in treatment group n = 21)</td>
<td>17% (17)</td>
</tr>
<tr>
<td>Pell [34]</td>
<td>1993</td>
<td>24 tibial and femoral nailings</td>
<td>Significant emboli 41% (10), FES 12.5% (3)</td>
<td>4.1% (1)</td>
</tr>
<tr>
<td>Behn [35]</td>
<td>1997</td>
<td>Consecutive post-mortem examinations</td>
<td>Emboli seen during 87% (97)</td>
<td>4.1% (1)</td>
</tr>
<tr>
<td>Hiss [36]</td>
<td>1996</td>
<td>Review of 53 blunt trauma deaths</td>
<td>Significant emboli 41% (10), FES 12.5% (3)</td>
<td>17% (92) of all cases</td>
</tr>
<tr>
<td>Maxeiner [37]</td>
<td>1995</td>
<td>Retrospective analysis of deaths after total hip replacement</td>
<td>60.4% (32)</td>
<td>0.25% (9)</td>
</tr>
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in 97 procedures [33]. Severe episodes were commonest during instrumentation of pathological fractures (59% of these procedures) and coincided with decreases in arterial oxygen saturation. TOE has demonstrated that embolic showers may continue postoperatively and tend to fragment causing pulmonary embolisation. The emboli may also coalesce forming thrombotic masses. Emboli of between 1 and 8 cm in diameter were seen and this was associated with patients developing FES [34]. In one patient, a large embolic load to the right heart was seen on TOE; ultimately, when the patient died, there was no evidence of fat macroemboli at post-mortem.

Incidence using post-mortem evidence
Post-mortem studies show a markedly different and very high incidence of FE. A study of 527 autopsies found evidence of FE in 92 [35]. Maxeiner examined 130 deaths after hip fracture and found FE responsible for at least six deaths (three intra-operatively and three postoperatively), and contributory in nine other deaths [37]. A report of the examinations of 53 victims of fatal beatings found a high incidence [36]. These young men were murder victims and suffered severe blunt trauma within the 24 h preceding autopsy. Thirty-two cases showed FE to major organs with no other cause for death. The authors hypothesised that the source of the FE was mechanical disintegration of the subcutaneous adipose tissue.

The agreement between post-mortem and clinical findings is poor and this disparity has given rise to the concept of the ‘iceberg effect of FE’ [8]. The issue has been further complicated by the use of echocardiography and BAL that suggest a high incidence of FE in the circulation. FE may be common whilst FES relatively rare.

Predisposition
The incidence of FE is undoubtedly highest following trauma, particularly lower limb fractures; however, FES is reported in many other conditions (Table 4) and the difficulty in these cases is the lack of a consistent and reliable standard for diagnosis. Procedures such as liposuction which deliberately disrupt both fat and blood vessels might result in FES; however, the reported incidence is very low [42–44]. FES occurs with hepatic necrosis and fatty liver [48, 49]. In these circumstances, protracted fat embolisation from damaged hepatocytes may be involved. Both lipid and propofol infusions have been reported to be associated with subsequent respiratory failure but not all the other features of FES [40, 46]. The mechanism may be different in that fat emulsions can produce exogenous fat overload leading to mechanical obstruction of the vascular tree and local damage.

FES is recognised as part of an acute sickle cell crisis [17, 23, 56]. Acute chest syndrome is the second most common reason for hospital admission and leading cause of death in sickle cell disease. This syndrome is characterised by cough, dyspnoea and chest pain and has been attributed to many causes including FE, pulmonary infarction, hyperventilation secondary to rib infarcts or pneumonitis. Bone marrow necrosis caused by hypoxia and stasis during an acute crisis may release bone marrow fat. In 60% of acute chest syndrome cases, the pulmonary macrophages stain for fat [23] and this is associated with bone marrow infarction as shown by either isotope scanning or magnetic resonance imaging. Biochemical markers such as PLA₂ may increase up to 100 times the usual value found in patients with quiescent sickle cell disease and more than five times greater than a similar control group ill with pneumonia [17].

Pathophysiological mechanisms
No single theory satisfactorily explains all the pathophysiological features of FES as it is associated with a wide range of conditions (including some with no obvious evidence of bone marrow trauma) and has a number of differing presentations.

In floating theory
This traditional view of fat embolism suggests that fat is physically forced into the venous system following trauma [57]. The normal marrow pressure is 30–50 mmHg but can be increased up to 600 mmHg during intramedullary reaming [58]. Intramedullary devices are associated with

<table>
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<th>Table 4 Reported causes of fat embolism syndrome</th>
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<tr>
<td>Mechanical disruption to adipocytes</td>
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<td>Hepatic failure (fatty liver or necrosis) [48, 49]</td>
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higher pressures within the marrow cavity and more FE than extramedullary fixation [59, 60]. Ultrasonographically, most emboli occur during opening and manipulation of the intramedullary cavity [61]. Intramedullary fat content is important and previously reamed femurs are associated with extremely low incidence of FES-type problems because of reduced intramedullary fat [62]. Cement is associated with a much higher incidence of FE, although the incidence is not zero in uncemented prostheses [63]. Bone marrow injection in animal models consistently produces cardiorespiratory signs [64, 65] and FE can be induced experimentally by reaming and pressurising the intramedullary space with polymethylmethacrylate cement [66]. Sampling of femoral vein blood has localised the origin of fat macroglobules to the injured extremity [67].

Lipase theory
Trauma leads to an elevated plasma lipase titre which precedes any rise in FFAs [14]. This enzyme destabilises circulating fats by de-emulsification, saponification and mobilising lipid stores [68]. Kronke detected increases in serum lipase in 50–70% of patients with fractures and also a positive association between lipase titres and clinical manifestations of FE [69]. However, this rise was not found in another study [19].

Free fatty acid theory
A second biochemical theory invokes the histotoxic effects of FFAs which are known to cause severe vasculitis in animal models leading to haemorrhagic oedema and destruction of the pulmonary architecture within 6 h [70]. A flaw in this theory is that neutral fats are the major constituents of bone marrow and they do not display this effect [25]. However, it is highly likely that in vivo there is hydrolysis of neutral fats to FFAs and this may help explain the symptom-free interval before the onset of signs and symptoms during which hydrolysis occurs.

Shock and coagulation theory
This is based on the observation that many patients who develop FES are hypovolaemic secondary to multiple trauma or one of the other associated conditions. Hypovolaemia leads to a sluggish circulation with 'sludging' of blood components and microaggregate collection in the lungs. Trauma to the tissues exacerbates this by damage to the vascular intima leading to platelet activation. Bone marrow fat may then provide a surface on which activated platelets can adhere [71].

Systemic embolisation
A curious aspect of FES is the phenomenon of systemic embolisation without pulmonary effects [13, 28]. One suggestion is that this can occur via a patent foramen ovale, which has a prevalence of around 35% in the general population, and systemic embolisation via this route has been reported [1]. Alternatively, transpulmonary systemic fat embolisation has been demonstrated in dogs without a patent foramen ovale [72]. The deformability of the fat emboli coupled with the rise in pulmonary arterial blood pressure associated with FES may force the fat globules through the pulmonary capillary bed.

Relationship of fat embolism syndrome to multiple organ failure from other causes
Fat embolism syndrome shares many features characteristic of systemic inflammatory response syndrome and multiple organ failure from other causes. Bone marrow necrosis occurs in a wide variety of conditions such as bacterial infections and sepsis [73] and is associated with DIC [74]. Patients with the acute respiratory distress syndrome (ARDS) and sepsis often display fat in alveolar macrophages [24, 75]. PLA2 levels increase in ARDS and sepsis and this increase precedes the development of hypoxia and shock but correlates with clinical severity [76, 77]. A 62-fold increase in PLA2 has been recorded following trauma [78] and a 300-fold rise in sepsis with a significant correlation between decreasing P(O2)/FIO2 ratio and increasing PLA2 levels. PLA2 may rise as part of a stress response to trauma and has an excess of substrate in cases of marrow fat release. C-reactive protein (CRP) rises dramatically in critical illness. It causes agglutination of chylomicrons and very low-density lipoproteins [79]. With a combination of bone marrow infarction, rising PLA2 and CRP, FE may cause acute lung injury in some critically ill patients. This mechanism has been suggested in trauma patients (Fig. 1) [20, 71].

Treatment
Treatment is non-specific and supportive. Different approaches have been tried with varying success; however, the lack of universal diagnostic criteria and the small groups of patients studied make many of these trials difficult to interpret. Of paramount importance is the early resuscitation and stabilisation to minimise the stress response and hypovolaemia [71, 80].

The most common manifestation of FES is pulmonary dysfunction and for this reason any patient at risk should be closely monitored. The routine use of pulse oximetry may detect early hypoxaemia and allows prompt correction with controlled humidified oxygen therapy [81].
Lindeque found that patients with a $P_{O_2} < 9.2$ kPa on admission were twice as likely to develop hypoxaemia [5]. Whether early administration of oxygen actually prevents the onset of the syndrome by preventing hypoxaemia, further catecholamine response and fat mobilisation remains unclear. Between 10 and 44% of patients require mechanical ventilation but the pulmonary dysfunction caused by FES usually resolves in 3–7 days [6, 7, 38]. Corticosteroids have been studied extensively in FE in both animal models and humans. In theory, there are many ways in which they could act to prevent the onset of FES. Possible beneficial effects include stabilisation of the pulmonary capillary membrane, thus reducing the leak that creates interstitial oedema, blunting the inflammatory response, stabilising complement system activation and retarding platelet aggregation [68]. Studies reporting beneficial effects [5, 31, 82, 83] used doses of methyl prednisolone between 9 mg.kg$^{-1}$ and 90 mg.kg$^{-1}$ (in divided doses). The results of these trials were impressive, with a 10-fold reduction of FES in one series; however, the only fatality reported in any of these trials was due to overwhelming sepsis in a patient receiving corticosteroids [30]. All these randomised controlled trials report significant decreases in FES, although only three [5, 30, 82] reported significantly improved gas exchange. The numbers of patients treated are small, ranging between 10 and 40 in the treatment groups, and factors including temperature and white cell count, which would be altered by corticosteroids themselves, were used as indicators of FES. On the contrary, other work suggests that methyl prednisolone does not modify pulmonary hypertension and prostenoid response [84]. Further work is required to elucidate the optimum timing of administration of corticosteroid therapy and most importantly its outcome.

Heparin is known to clear lipaemic serum by stimulating lipase activity and has been advocated for treatment of FES. However, the evidence for heparin treatment in FES is contradictory [85, 86]. If increases in FFAs are an important part of the pathogenesis of FES, then activation of lipase is a potentially dangerous therapeutic intervention. Furthermore, the risk of bleeding, even with low-dose heparin, cannot be ignored in patients with multiple injuries. Prevention of FFA mobilisation by providing adequate glucose has been used as a prophylactic strategy [87]. Alcohol decreases serum lipase activity. FES has been found to be less common in accident victims whose blood alcohol levels were greater than 0.03 g.dl$^{-1}$ compared with those with blood levels $<0.02$ g.dl$^{-1}$ [32]. However, the relationship between blood alcohol levels, FFA levels and the development of FES may not be casual [88]. Aspirin has been recommended as a prophylactic agent as it prevents...
Gas exchange abnormalities [82]. Aspirin blocks the production of thromboxane which occurs in animal models of FE [64, 89]. Dextran has been rejected because of problems with coagulation and renal function. Aspirin, heparin and dextrans reduce the platelet adhesiveness and thus reduce the formation of microaggregates [74].

**Surgical strategies for preventing FES**

Surgical fixation of fractures increases intramedullary pressure and causes mobilisation of marrow fat [60]. The relationship between intramedullary pressure and FE has led to the development of specific strategies in trauma surgery [90]. External fixation or fixation with a plate produces less lung injury than intramedullary fixation [66]. After reaming, the pressure generated during nail insertion is similar to that produced by an unreamed nail but the incidence of FE has been shown to be lower when unreamed nails are used. The tools themselves may play a role as blunt reamers produce much higher pressures than sharp reamers [91] and hollow nails produce far lower pressures than solid ones [92]. Repeatedly pushing and pulling the reamer may also result in high-pressure peaks [93]. Ultrasonic reamers used in revision arthroplasty significantly increase the showers of emboli seen by TOE [94]. Venting the medullary canal reduces the emboli during the insertion of the femoral component of hip arthroplasty [95]. Intramedullary ligation has been shown to reduce the incidence of hypotension, pulmonary fat deposition and arachidonic acid metabolites if used prior to cement and prosthesis insertion [96]. Timing of the operative procedure appears to be important. Pulmonary complications are increased and hospital stay lengthened in patients with multiple injuries in whom fixation is delayed for more than 24 h [97–99]. However, early nailing may not be advantageous in patients with thoracic trauma as there may be increased lung injury with this approach [100].

**Summary**

Fat embolism is frequently found when actively sought but seldom produces all the classical clinical signs of respiratory failure, petechial rash and pyrexia. Additional factors such as hypoxaemia and catecholamine release may be required to produce FES, and fatty acid release resulting from bone marrow damage are only one aspect of an exaggerated inflammatory response. Despite the many therapeutic interventions tried, the only one proven in randomised controlled trials is corticosteroids but the currently available literature is inadequate to recommend corticosteroids for either treatment or prophylaxis. The cornerstone of treatment is preventing the stress response, hypovolaemia and hypoxia and then operative stabilisation of fractures within 24 h in the absence of chest trauma. It may well be that with current advanced trauma life support guidelines on the early use of intravenous fluids, high-flow oxygen and analgesia, the incidence of FES has decreased. There are few prospective studies in the literature and more recent results from centres providing appropriate early resuscitative and surgical intervention are needed. Further studies are required to elucidate the role of FE in the genesis of acute lung injury and multiple organ failure in critical illness.

**References**


Monitoring of pulmonary mechanics in acute respiratory distress syndrome to titrate therapy
Luciano Gattinoni, Carlesso Eleonora and Pietro Caironi

Purpose of review
This paper reviews recent findings regarding the respiratory mechanics during acute respiratory distress syndrome as a tool for tailor its ventilatory management.

Recent findings
The pressure—volume curve has been used for many years as a descriptor of the respiratory mechanics in patients affected by acute respiratory distress syndrome. The use of the sigmoidal equation introduced by Venegas for the analysis of the pressure—volume curve seems to be the most rigorous mathematical approach to assessing lung mechanics. Increasing attention has been focused on the deflation limb for titration of positive end-expiratory pressure. Based on physiologic reasoning, a novel parameter, the stress index, has been proposed for tailoring a safe mechanical ventilation, although its clinical impact has still to be proved. Evidence has confirmed that a variety of underlying pathologies may lead to acute respiratory distress syndrome, making unrealistic any attempt to unify the ventilatory approach. Although extensively proposed to tailor mechanical ventilation during acute respiratory distress syndrome, there is no evidence that the pressure—volume curve may be useful in setting a lung-protective strategy in the presence of different potentials for recruitment.

Summary
The Venegas approach should be the standard analysis of pressure—volume curves. In any patient, the potential for recruitment should be assessed, as a basis for tailoring the most effective mechanical ventilation. Further studies are needed to clarify the potential use of the pressure—volume curve to guide a lung-protective ventilatory strategy.

Keywords
acute lung injury, acute respiratory distress syndrome, lung recruitment, positive end-expiratory pressure, pressure-volume curve, respiratory mechanics

Abbreviations
ARDS acute respiratory distress syndrome
PEEP positive end-expiratory pressure
PV pressure—volume
VT tidal volume

Introduction
Since the first description of acute respiratory distress syndrome (ARDS) in 1967 [1], lung mechanics have had a central role both in understanding the pathophysiology of the syndrome and in tailoring the ventilatory therapy in patients affected by this disease. Before discussing the most recent findings in this field, we believe it is useful to provide a brief summary of its evolution over the years.

Lung mechanics: pathophysiology
The ARDS lung was first described as ‘stiff’, suggesting that the basic elastic structure of the ARDS lung parenchyma is altered, likely as a consequence of increased fibrosis. After about 20 years, however, it has been clearly demonstrated that the decreased compliance of the respiratory system is not related to a decreased lung elasticity but primarily to the reduction of lung gas volume (the ‘baby lung’ concept) [2]. It follows that the specific lung compliance, i.e., the lung compliance normalized for the resting lung gas volume, is nearly normal in the ARDS lung and similar to specific lung compliance in healthy patients [2,3].

A second step in understanding lung mechanics in ARDS was the recognition of the importance and the role of the chest wall compliance. For many years, modifications of the compliance of the respiratory system have been only attributed to the changes in lung compliance. It has recently been recognized that the chest wall compliance may be deeply altered in ARDS patients [4–7]. In fact, in a consistent fraction of these patients, intra-abdominal pressure is abnormally elevated, which, in turn, decreases the chest wall compliance [8,9]. These observations have considerable consequences. It follows that for the same pressure applied to the respiratory system, the transpulmonary pressure (the real distending force of the lung) may be completely different depending on the pleural pressure, which in turn is affected by the chest wall compliance [10].

A third major step regarded the pressure—volume (PV) curve of the respiratory system, one of the most used and important descriptors of the respiratory mechanics.
It has been recently recognized, both in theoretical [11] and in experimental and clinical studies [12,13], that the PV curve of the ARDS lung is similar to a recruitment—pressure curve, clearly indicating that alveolar recruitment is an inspiratory phenomenon occurring along the entire PV curve. This phenomenon is now widely recognized [14]. It is important to emphasize, however, that the recruitment—pressure curve reflects the percentage of the potential for recruitment achieved at each airway pressure applied, i.e., the fraction of the total amount of recruitable tissue (usually assessed between 0–45 cmH₂O applied airway pressure) and not the actual amount of tissue recruited [13]. Consequently, the fraction of alveolar recruitment may be the same, at a given airway pressure, in the presence of a small or large potential for recruitment.

**Lung mechanics: pressure—volume curve analysis**

**Measurement of pressure—volume curve**

The first method proposed for measuring the PV curve was the stepwise inflation method, consisting in a stepwise lung inflation by using a supersyringe [15]. This method assumes that the volume displacement of the thorax–lung complex is equal to the volume inflated from the supersyringe into the respiratory system. Unfortunately, this is not the case: in recent years, several correction factors have been proposed for various modifications occurring in the respiratory system while performing this measurement (temperature and pressure changes, humidity, O₂ consumption / CO₂ production) [16], but they have not yet found general application. A second method has been proposed to assess PV curve (the continuous slow-flow method) [17]. This method does not theoretically avoid the influence of O₂ consumption, one of the most important artifacts of PV curve measurement, however. In contrast, the interrupter technique with multiple occlusions [18] might minimize the artifacts due to the gas exchange.

Mehta *et al.* [19] investigated the reproducibility of the PV curve over time and compared the stepwise inflation method with the multiple occlusion technique. Consistent with what was already demonstrated [20,21], they found a reasonable reproducibility over time and similar values of lower inflation and upper inflation points between the two methods, concluding that the two techniques are similar, in the daily assessment of PV curve. To avoid some of the problems associated with the supersyringe technique, as in the disconnection from the ventilator, Albaiceta *et al.* [22] proposed tracing the PV curve, during both inspiration and expiration, by incremental increases or decreases in continuous positive airway pressure. To assess lung volume changes, the inductive plethysmography method was used. Similarly, Nunes *et al.* [23], using inductive plethysmography for volume signals and the inspiratory occlusion technique for airway pressure measurements, investigated the PV curve at different levels of positive end-expiratory pressure (PEEP) and at different tidal volumes (VTₚ). These authors confirmed that alveolar recruitment is an inspiratory phenomenon occurring along the entire PV curve independently on the lower and upper inflection point and that inductive plethysmography may be a useful technique to assess lung recruitment.

In our opinion these three last reports [19,22,23] confirmed our previous knowledge but, unfortunately, all referred to the mechanics of the whole respiratory system, without considering its individual components, i.e., lung and chest wall mechanics, which may be particularly important in shaping the PV curve [7]. Both Nunes *et al.* [23] and Albaiceta *et al.* [22], moreover, implicitly assumed the thoracic wall changes as equivalent of gas lung volume changes. This equivalence will be true in the absence of any blood shift from thoracic compartment to the periphery and vice versa. Our preliminary data suggest that the blood shift during PV curve measurement may be quite relevant and may have the same magnitude of lung recruitment [24,25]. We believe that the relation between modifications of chest wall volume, lung volume, and blood shift during PV curve assessment need further investigation, especially when the PV curve is used to estimate pulmonary recruitment.

**Interpreting pressure—volume curve**

Several parameters derived from the PV curve have been considered of potential clinical interest, such as the lower inflection point, the upper inflection point, and others (Fig. 1). Initially these parameters were manually identified. In an attempt to standardize their definitions, the lower and the upper inflection point were computed as the point of intersection of the ‘inflation’ compliance (or chord compliance) and, respectively, the starting and ‘final compliance’. Roupie *et al.* [26] defined as ‘final compliance’ the portion of PV curve in which compliance is decreased at least 20%, whereas Nunes *et al.* [23] suggested a threshold of 10%.

A standardized method to evaluate PV curve parameters was proposed by Venegas *et al.* [27]. His approach, applicable both to the inspiratory and expiratory limb of the PV curve, is based on fitting the PV curve with the following equation:

\[ V = a + b \cdot \left[ 1 - e^{-(P-c)/d} \right]^{-1} \]

where \( V \) is the volume inflated and \( P \) is the pressure generated (see Fig. 2 for parameters). We consider this approach the most rigorous available. Unfortunately, it implies a change of nomenclature, which may generate a further confusion on the topic. In fact, the lower and upper inflection points, according to the Venegas approach, are named ‘lower’ and ‘upper’ corner, respectively,
whereas the inflection point is defined as the point of maximal compliance, where the sigmoid changes its curvature (mathematical inflection point). The original Venegas approach [27], slightly modified in a following paper by Harris et al. [28], has been increasingly used in the recent literature.

Pereira et al. [29] applied the Venegas equation to the inflation and deflation limbs of the lung and chest wall PV curves in 36 consecutive patients with acute lung injury. An excellent fit of the equation was found in every patient. In some patients, a lower inflection point on the chest wall PV curve was identified (which was called \( P_{mci, w} \), point of maximum increase of chest wall compliance), but in contrast with Mergoni et al. [7], its contribution to the lower inflection point of the respiratory system PV curve was limited. Six patients, subsequently excluded from the study, however, interestingly presented a negative value of \( P_{mci} \) (either in the lung or the chest wall component). The same results were described by Bayle et al. [30] in an animal model. The physiologic meaning of this finding must be further elucidated.

Markhorst et al. [31] proposed an evolution of the Hickling mathematical model [11], taking into account also air trapping, degree of alveolar recruitability, ARDS severity, and chest wall characteristics. In their model, PV curve was analyzed by fitting the curve with the Venegas equation [27,28]. After several simulations, the authors concluded that the PV curve analysis does not predict optimal airway pressure values (plateau pressure and PEEP) needed to recruit previously collapsed alveoli and to prevent alveolar derecruitment.

Indeed, where PV curve interpretation is concerned, the Venegas approach seems to provide a reliable and objective method to assess different PV curve parameters, both in humans and in experimental models. Unfortunately, the physiologic meaning of these variables is still unclear. Moreover, the change in nomenclature should be fully acknowledged to avoid further confusion (Fig. 1).

**Lung mechanics and therapy**

Besides its role in the pathophysiology of ARDS, lung mechanics has been used to titrate the ventilatory therapy of patients affected by this syndrome. Initially, the main interest was directed towards the interaction between lung
mechanics and gas exchange, whereas recently several investigations have been focused on the interaction between lung mechanics and lung-protective ventilatory strategies.

Respiratory mechanics and gas exchange
Since the first description of ARDS, PEEP application has been aimed at improving oxygenation. In association with this benefit, a reduction in cardiac output has been recognized as the main side effect, because of a marked increase in intrathoracic pressures following PEEP increase. The first paper addressing this topic in a clinical structured fashion by Suter et al. [32] found that the ‘best’ PEEP value, defined as the PEEP level associated with the best oxygen delivery (cardiac output × arterial oxygen content), was associated with the greatest respiratory system compliance recorded. Following the same arguments, Lemaire et al. [33] and other investigators [21,34–36] proposed, as the best compromise between oxygenation improvement and hemodynamic impairment, to titrate PEEP level 2 cmH2O above the lower inflection point of the PV curve (minimal PEEP). This approach was used by Amato et al. [37] to compare a lung-protective strategy (with low VT and relatively high PEEP) and a conventional ventilatory strategy (with higher VT and lower PEEP), during the ventilation of ARDS patients. The rationale of this approach leans on two considerations: titrating PEEP on the PV curve is the best compromise between oxygenation and hemodynamic deterioration, to titrate PEEP value = 2 cmH2O above the lower inflection point is sufficient to ‘keep the lung open’. Several caveats, however, must be considered. First, oxygenation improvement does not necessarily imply alveolar recruitment but may simply reflect cardiac output decrease and pulmonary blood flow ‘redistribution’ [38]. Second, it is now questionable whether the inspiratory lower inflection point represents a marker of ‘open lung’. In fact, lung recruitment occurs well above the lower inflection point, and, more important, is an inspiratory phenomenon [13], whereas PEEP acts on the expiratory portion of the PV curve [3].

The importance of the deflation limb of the PV curve, rather than the inspiratory limb, has been increasingly acknowledged. Albaiceta et al. [39••], in an excellent paper, combined PV curve analysis (by using the Venegas approach) and CT scan technology to assess lung morphology. Alveolar recruitment was confirmed to occur continuously and along the inspiratory limb of the PV curve. In contrast, the critical point for lung de-aeration and de-recruitment (lung collapse) was identified at airway pressures below the point of maximum curvature on the deflation limb. The same group of investigators reported differences in the deflation PV curves between pulmonary and extrapulmonary types of ARDS [40], adding evidence that, at least in the early phase, respiratory mechanics of the two syndromes may be different [9].

Respiratory mechanics and lung protection
In the view of the open lung approach, the potential impact of PEEP application in preventing ventilator-induced lung injury has been recently emphasized. The rationale for this approach is based on two observations. First, PEEP may prevent the cyclical intratidal opening and closing of the alveoli, which is considered to be deleterious for lung structures [41,42]; second, PEEP may decrease the intraparenchymal stress/strain distribution while keeping open otherwise collapsed lung regions, in accordance with the theory of Mead et al. [43]. There are considerable evidences, in both in-vitro and in-vivo studies, that PEEP may decrease the mechanically induced lung inflammation [44–47]. It has been recognized, however, that PEEP application leads, as side effect, to a global increase in alveolar stress and strain. The recent ALVEOLI trial [48], moreover, was unable to show differences in survival between a high and low PEEP approach. Indeed, we may expect that the ultimate effect of PEEP depends, in any given patient, on the balance between its putative beneficial effects (keeping lung open and preventing local mal-distribution of stress and strain) and detrimental effects (global increase of stress and strain).

Preventing the intratidal collapse
Under the perspective of preventing the intratidal collapse, Grasso et al. [49••] tested a new parameter, the stress index, to clinically identify the best compromise between alveolar recruitment and hyperinflation. The stress index (coefficient b) is the exponent of the equation correlating the airway pressure profile and the time during each VT [50]:

\[ \text{airway pressure} = a \times \text{time}^b + c \]

When \( b = 1 \), the relation is a straight line indicating a constant compliance throughout tidal inflation; when \( b < 1 \), the slope of the curve progressively decreases, i.e., the compliance progressively increases with tidal inflation; when \( b > 1 \), the slope of the curve progressively increases, indicating a decrease in compliance during tidal inflation. By using this approach, these investigators found, in an animal model of lavage-induced lung injury, that a stress index <1 was associated with intratidal recruitment, assessed by CT scan, whereas \( b > 1 \) was associated with hyperinflation. In conclusion, the authors suggested that it is safe to institute mechanical ventilation with a coefficient \( b = 1 \pm 10\% \). To set a stress index = 1, different combinations of VT and PEEP may be used. The hypothesis is fascinating. It is important to recognize, however, that the lavage-induced lung injury model is characterized by high potential for recruitment, although, as the authors acknowledge, the potential for recruitment in patients with ARDS may be highly variable. Accordingly, Vieillard-Baron et al. [51] found, through the traditional PV curve analysis, a limited potential for
recruitment in a group of ARDS patients with diffuse pneumonia (primary ARDS), in association with a markedly reduced compliance of the respiratory system.

**Keeping the lung open: the recruitment maneuver**

In the perspective of a lung-protective strategy based on the open lung approach, the recruitment maneuver may play a substantial role, and several papers have recently addressed this issue. Before discussing them, a few points should be clarified. First, the recruitment maneuver should be a procedure specifically designed to reach an opening pressure sufficient to open the ‘sticky’ atelectasis, i.e., the collapsed lung regions with higher opening pressures [52]. Furthermore, in a given patient, we should know the values of opening pressures and the total amount of ‘sticky atelectasis’. The second part of the problem, however, is to know how much airway pressure is necessary to keep open the previously collapsed lung regions, and, more important, whether it is worthwhile to do so.

Lim et al. [53] compared three different recruitment maneuver techniques (sustained inflation, pressure control ventilation, and incremental PEEP application). After the recruitment maneuver, different PEEP levels were applied. Three different experimental models were studied: lung injury induced by oleic acid injection, by mechanical ventilation, and by pneumococcal pneumonia. Recruitment maneuvers performed by pressure control ventilation (45 cmH₂O) appeared to be equivalent or superior to those performed by sustained inflation. Furthermore, the increase in PEEP after the recruitment maneuver aimed at preventing lung collapse was more effective in oleic acid- and ventilator-induced lung injury than in pneumonia-induced lung injury. In our opinion, as also discussed by the authors, these results may be explained by taking into account the different lung morphology of the three models. The oleic acid–induced lung injury model is characterized by a substantial increase in lung weight with a consequent formation of compression atelectasis, resulting in a high potential for recruitment [12,54]. These morphologic features may explain the effectiveness of recruitment maneuvers associated with PEEP application. It is conceivable that recruitment maneuvers open up collapsed lung regions and that increases in PEEP keeps them opened, counteracting the compressive forces of the diseased lung parenchyma. At the other end of the spectrum, the pneumonia-induced lung injury model is characterized by a low potential for recruitment, likely because of the prevalence of consolidated lung regions, in both animals [55] and humans [9]. Although even in patients with pneumonia-induced ARDS ‘sticky atelectasis’ may be present and recruitable, their absolute amount is usually very low (about 10% of lung parenchyma) [13]. In this context, the lack of effective response of recruitment maneuvers in pneumonia-induced lung injury models is easily explainable. In clinical perspective, analogous differences in patient population may explain some contradictory results [56,57]. Similarly, the variability of the underlying pathologic alteration may also clarify the negative results obtained in an unselected large population of ARDS patients [58]. Indeed, in our opinion, a growing body of evidence justifies the use of recruitment maneuvers only in patients with high potential for recruitment, in whom, after the maneuver, the PEEP level has to be increased.

Although the trend is to pursue the open lung approach, in our opinion the necessity to recruit the lung at any costs is not to be taken for granted. In other words, if the ‘sticky lung regions’ are not reopened at ‘safe’ airway pressures and are closed throughout the respiratory cycle, is it mandatory to recruit them while paying, as a price, high plateau pressures to open them, and higher PEEP to keep them open? We believe that this possibility can not be excluded a priori. Future studies are necessary to clearly address this issue.

**Conclusion**

New insights have been gained recently in the monitoring of respiratory mechanics during ARDS and in its use to tailor ventilatory management in these patients. The analysis of PV curve according to the Venegas approach seems to be the reference mathematical model for objectively assessing lung mechanics. The importance of the deflation limb for PEEP titration is becoming recognized. Although far from clinically proved, the use of novel parameters to tailor a safe mechanical ventilation, such as the stress index, fits well with our physiologic reasoning. It has been increasingly recognized that a variety of underlying pathologies may lead to ARDS, making unrealistic any attempt to unify our ventilatory approach. Although the PV curve has been extensively proposed to tailor ventilatory therapy for ARDS patients, we lack, at the moment, studies specifically addressing the use of the PV curve to set the lung-protective strategy in the presence of different potentials for recruitment. A good example is the paper by Amato et al. [37]. In this study, the group of patients randomly assigned to the lung-protective strategy used a PEEP level titrated 2 cmH₂O above the lower inflection point. In the absence of a lower inflection point, the PEEP was set at an arbitrary value of 15 cmH₂O. This assumption clearly highlights the lack we have of a physiologic approach to titrate PEEP level during mechanical ventilation and may help to explain the failure of the ALVEOLI study [48].

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Pulmonary mechanics in acute respiratory distress Gattinoni et al. 257


40 Idealzation on the lower inflection point of the PV curve comparing the Venegas approach and CT scan technology to assess lung recruitment and morphology in patients with early acute lung injury.


