Clinical Aspects of Respiratory Muscle Dysfunction in the Critically Ill
Michael I. Polkey and John Moxham
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When the load placed on the respiratory muscle pump exceeds its capacity, ventilatory failure ensues. This situation is ultimately fatal unless either medical therapy is able to reduce the load or mechanical ventilation is instituted. Preexisting neuromuscular disease is sometimes the primary indication for mechanical ventilation, but the more usual indications, at least in the general ICU setting, are nonneurologic causes, for example, trauma, surgery, and sepsis, in patients not previously known to have neurologic disease.

In recent years, perhaps because of the improved delivery of supportive therapies, there has been increasing interest in the occurrence of neuromuscular dysfunction as a consequence of prolonged ICU admission. For example, a MEDLINE search that sought citations referring to both critical illness/care and respiratory or limb muscle/nerve yielded no citations for the years 1966 to 1984, 3 citations for 1985 to 1990, 36 citations for 1985 to 1990, 36 citations for 1991 to 1995, and 71 citations from 1995 onward. Disease processes affecting peripheral nerves or muscles are likely to involve the respiratory muscles and, because adequate performance of the respiratory muscle pump is a prerequisite for successful liberation from mechanical ventilation, we would argue that assessment of the respiratory muscle pump in the ICU is of clinical importance.

In this article, we first review relevant normal respiratory muscle physiology and discuss the assessment of respiratory muscles in the ICU environment. We then review available data concerning acquired respiratory muscle dysfunction in the ICU, including critical illness neuromuscular abnormalities (CINMAs). Although preexisting neurologic disease can cause ventilatory failure, this occurrence is not considered in this article because we and others have reviewed this area.2–4

Estimation of Load

The focus of this article is on the capacity of the pump to respond to the load imposed by disease. Although pump performance is our main concern, it is relevant to consider how best to measure load in the ICU. The load may be increased either because the patient needs to increase minute ventilation to ensure adequate oxygenation or because the pressure changes required to achieve a given minute ventilation are increased (for example, in acute lung injury). Although most clinicians have an empirical feeling for the former, measurements of the latter are rarely made in the ICU.

The mechanical load comprises both the elastic load of the respiratory system (its compliance) that is present even without gas flow and airway resistance that is related to the flow of gas. The elastic load is measured by measuring respiratory system compliance, while the resistive load is measured by measuring airway resistance. While both of these quantities can be measured fairly easily in anesthetized and paralyzed patients, for example, using the interrupter technique, they are more difficult to measure in patients who are spontaneously breathing or are using pressure support in an attempt to wean...
from mechanical ventilation because they require the patients to totally relax their respiratory muscles. However, some investigators consider that the residual contribution of the respiratory muscles when the patient attempts to relax is clinically insignificant. In this situation, a clinically useful estimate of the load placed on the respiratory muscle pump may be made by measuring the dynamic compliance and/or the esophageal pressure (Pes) or transdiaphragmatic pressure (Pdi) time products during spontaneous respiration. The dynamic compliance is measured as the tidal volume divided by the Pes swing required to generate this tidal volume. Our practice is to take the mean of three representative breaths. The measurement assumes that muscles are inactive at end expiration and end inspiration, which clearly limits its extrapolation to many ICU patients, especially those with active abdominal muscles.

The Normal Respiratory Muscle Pump

Structure

The respiratory muscle pump may be considered to have an inspiratory and expiratory component. Although the expiratory muscles are critical for an effective cough, their failure in isolation is not normally considered a cause of ventilator dependence. Of the inspiratory muscles, the most important in healthy humans is the diaphragm, which during quiet respiration accounts for 60 to 70% of lung volume change. The extradiaphragmatic inspiratory muscles comprise the scalenes and parasternal intercostals, which are invariably active even during quiet breathing in healthy subjects, and the sternomastoids, which are recruited in response to increased load.

Physiology

Skeletal muscle (including respiratory muscle) is controlled by impulses conducted by motoneurons originating in the anterior horn of the spinal cord to the motor end plate that abuts the muscle fibers. Release of acetylcholine from the motor end plate depolarizes the muscle cell membrane. This depolarization is, in turn, directed inward to the sarcoplasmatic reticulum, causing intracellular calcium release that permits the cyclic attachment and detachment of bridges between actin and myosin that, in turn, results in contraction of the muscle fiber (for a review, see Jones). This produces either tension generation, if the muscle is kept isometric, or shortening, if the muscle is free to move. The force generated by muscle contraction is related to the number of fibers stimulated, the frequency of stimulation, the length of the muscle at the time of stimulation, and the degree of freedom of movement that it has. These considerations give rise to the force-frequency, force-length, and force-velocity relationships, respectively. Of these, the force-length and force-frequency relationships are of greatest clinical relevance.

An understanding of the force-frequency relationship (Fig 1; see also Cooper and Eccles) is worthwhile because it assists the understanding of the clinical application of muscle physiology. In essence, a single impulse traveling down the nerve results in a single twitch (Tw) that has the two discrete components of contraction and relaxation. If stimuli are applied with an increased frequency such that full relaxation has not occurred, then the addition of tension occurs and a muscle tension greater than the single Tw is obtained with a sawtooth appearance. If the stimulus frequency is increased further, the Tws fuse to create a tetanus. The plot of tension (or, for the diaphragm, Pdi) against stimulus frequency is termed the force-frequency curve. The shape of the force-frequency curve is influenced by a number of factors, including muscle length and fatigue. In limb muscle, the tension elicited by high stimulation frequencies (the tetanic tension) is the pressure elicited by a maximal voluntary effort.

The force-length relationship is relevant to the critically ill patient because lung volume is commonly altered by disease or by the application of positive end-expiratory pressure. Diaphragm length is reduced by hyperinflation, and as a consequence,
whether assessed by volitional or nonvolitional methods, its pressure-generating capacity is diminished.\textsuperscript{20–22} As shown in Figure 2, acute hyperinflation results in a reduction in diaphragm force generation, expressed as Pdi, in response to both low-frequency stimuli\textsuperscript{22,23} and high-frequency stimuli\textsuperscript{24} as well as to voluntary maneuvers.\textsuperscript{21} Similarly, the tension-generating capacity of the diaphragm also is reduced in chronic and acute-on-chronic hyperinflation, although the magnitude of this effect remains a moot point.\textsuperscript{25–27} However, it is perhaps less widely appreciated that the reduction in Tw Pdi that follows both acute and chronic hyperinflation results principally from a reduction in the ability of the diaphragm to lower intrathoracic pressure, which is estimated from the Pes (Fig 2).\textsuperscript{22,23,27} Moreover, like other skeletal muscle, the diaphragm exhibits length dependence of activation such that at high lung volumes, there is a disproportionate reduction in the pressure elicited by low (physiologic) stimulation frequencies.\textsuperscript{24} The clinical significance of these data is that a patient with airflow obstruction and dynamic hyperinflation would be expected to have ineffective diaphragm action for the three following reasons: first, the absolute force-generating capacity of the diaphragm is diminished; second, the force at physiologic firing frequencies (10 to 20 Hz) is disproportionately diminished; and third, the proportion of tension that is translated into reducing intrathoracic pressure is particularly reduced.

**Assessment of the Respiratory Muscles**

Structurally, the respiratory muscles are skeletal muscles\textsuperscript{28,29} and are, therefore, vulnerable to the same diseases and physiologic processes as, for example, the quadriceps or adductor pollicis (AP) muscles. However, in contrast to the peripheral muscles, their assessment can be problematic by virtue of their location. Established techniques for the measurement of respiratory muscle strength (as pressure) \textit{in vivo} only exist for the diaphragm, although techniques also have been described for the sternomastoid\textsuperscript{30} and the abdominal muscles.\textsuperscript{31,32} Similarly, electrophysiologic data are also principally obtained from the phrenic nerve and diaphragm.

**Pressure Generation**

A summary of tests together with average values and values used to exclude muscle weakness is shown in Table 1. The function of the inspiratory muscles is to create a negative pressure in the thorax, and, apart from the vital capacity,\textsuperscript{33} the most widely used measure of inspiratory muscle strength is the measurement of pressure generated in the nostril\textsuperscript{34,35} or mouth\textsuperscript{36,37} during a maximal voluntary maneuver. These measurements are a global reflection of inspiratory muscle action. The only respiratory muscle for which tension (as pressure) is commonly measured is the diaphragm. The action of the diaphragm is to lower pressure within the thorax and to raise it within the abdomen, and Pdi, therefore, is measured as the difference between gastric pressure (Pga) and Pes. An example is shown in Figure 3. The measurement of Pdi has become the “gold standard” in respiratory muscle physiology both because the diaphragm is the most important inspiratory muscle\textsuperscript{12} and because it is the only one in which measurements of tension can be made after selective nerve stimulation.

Clearly, the reliability of the calculated Pdi depends on the accurate measurement of Pes and Pga and also on the assumption that Pes is a true reflection of intrathoracic pressure and Pga is a true
reflection of intraabdominal pressure. That Pes and Pga are indeed valid measures was established by studies comparing them with directly measured pleural pressure and pressure measured in the abdomen. A choice of the following catheters is available for recording Pes and Pgas: air-filled, water perfused, and solid-state. Catheter choice is largely a matter of personal preference; however, it is important that the equipment used has an adequate frequency response (i.e., >10 Hz) and that the recording equipment be calibrated before each session. For air-filled balloons, it should be noted that more air may need to be placed in the esophageal balloon if the patient is, as is usual in the ICU, supine. While placement of catheters is straightforward in self-ventilating patients, it can be more difficult when a tracheostomy or endotracheal tube (ETT) is in place. This is discussed in greater detail below.

As well as the maximal static effort, a variety of alternative inspiratory maneuvers are possible and may be combined with the measurement of nasal, nasopharyngeal, esophageal, or transdiaphragmatic pressures. However, all these tests require the patient to make a maximal effort and are, therefore, of limited value in the ICU, unless the results are unequivocally normal. Thus, even when evaluated in nonsedated patients in the ICU, the maximal inspiratory pressure (Pmax) was shown to significantly underestimate inspiratory muscle strength when repeat measurements were made by the same or different observers. Some investigators hypothesize that the value of Pmax in the ICU can be enhanced by the use of a unidirectional valve placed in the circuit such that the patient is allowed to expire but inspires against an occluded airway. An alternative to voluntary efforts is to measure the Pdi or mouth/ETT pressure (Pet) in response to a single bilateral supramaximal phrenic nerve stimulation, a Tw. This approach has the great advantage that the results are independent of patient aptitude and motivation. In theory, the most complete data would be obtained by constructing the complete force-frequency curve of the diaphragm using bilateral trains of stimuli at different frequencies. However, such stimulation, if supramaximal (see below), is barely tolerable in humans outside the laboratory situation. Accordingly, it seems likely that for the foreseeable future, the majority of data will be obtained using single stimuli. This caveat does not apply to patients who have implanted diaphragm pacemakers who can tolerate tetanic stimuli given via the pacemaker, indicating that the problem with tetanic stimulation is, at least in part, the stimulation mode. Repetitive magnetic stimulators are currently being developed, and their use to construct in vivo

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Lower Limit of Normal, cm H_2O</th>
<th>Study/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pmax</td>
<td>Quick, no catheters; normal values in large series</td>
<td>Inaccurate in ICU</td>
<td>60 (F)</td>
<td>Enright et al 1994</td>
</tr>
<tr>
<td>Pmax</td>
<td>Quick, no catheters; normal values in large series</td>
<td>Inaccurate in ICU</td>
<td>80 (M)</td>
<td></td>
</tr>
<tr>
<td>SNIP</td>
<td>Quick, no catheters</td>
<td>Not suitable for patients using ETT or tracheostomy</td>
<td>70 (M)</td>
<td>Uldry and Fitting 1995</td>
</tr>
<tr>
<td>Sn Pes</td>
<td>Direct measure of intrathoracic pressure</td>
<td>ETT or tracheostomy must be occluded; requires cooperative patient; catheters required</td>
<td>60 (F)</td>
<td></td>
</tr>
<tr>
<td>Sn Pdi</td>
<td>Direct measure of Pdi</td>
<td>ETT or tracheostomy must be occluded; requires cooperative patient; catheters required</td>
<td>70 (M)</td>
<td></td>
</tr>
<tr>
<td>BAMPS-Tw Pdi</td>
<td>Independent of motivation; direct measure of diaphragm contractility</td>
<td>ETT or tracheostomy must be occluded; lung volume and potentiation considerations; catheters required</td>
<td>20 (M and F)</td>
<td>Mills et al 1996</td>
</tr>
<tr>
<td>BAMPS-Tw Pet</td>
<td>Independent of motivation; direct measure of diaphragm contractility</td>
<td>ETT or tracheostomy must be occluded; lung volume and potentiation considerations</td>
<td>20 (M and F)</td>
<td>Mills et al 1996</td>
</tr>
<tr>
<td>UMS-Tw Pdi</td>
<td>Independent of motivation; direct measure of diaphragm contractility; can diagnose local etiologies (e.g., postsurgical)</td>
<td>ETT or tracheostomy must be occluded; lung volume and potentiation considerations; catheters required</td>
<td>10 (L)</td>
<td>Mills et al 1995</td>
</tr>
</tbody>
</table>

*Pmax = maximal expiratory pressure; SNIP = sniff nasal inspiratory pressure; Sn = sniff; F = female; M = male; L = left hemidiaphragm; R = right hemidiaphragm.
force-frequency curves of the diaphragm in the future cannot be ruled out.

Our current preference is to measure Tw Pdi. Unfortunately, the placement of esophageal and gastric balloons in intubated patients is not always possible without the use of sedative drugs (although we have found placement under direct vision using a bronchoscope positioned in the pharynx a viable alternative in a minority of patients). In this situation, the investigator must sedate the patients using drugs the effect of which on diaphragm contractility is unknown and then either accept this limitation of the data or wait for the effects of the drugs to wear off. When it is not possible to pass balloon catheters, an alternative is to measure the Tw Pet by occluding the ETT at end expiration. We have constructed a valve for this purpose that synchronizes with our nerve stimulators.60 Although this approach has clear attractions, Tw mouth pressure (and, it is assumed, Tw Pet) is numerically similar to Tw Pes, rather than to Tw Pdi.61 The disadvantage of this approach is that if Tw Pdi is small, then, because Tw Pes is smaller than Tw Pdi (usually by 50 to 60%, depending on the stimulation modality), Tw Pet may be harder to measure accurately because the noise-to-signal ratio will be large. Similarly, increases in lung volume, as occur for example if positive end-expiratory pressure is applied, disproportionately influence Tw Pes and, therefore, Tw Pet. For the bilateral anterior magnetic phrenic nerve stimulation (BAMPS) technique, the diminution of Tw Pdi with increasing lung volume is 0.3 cm H2O per percentage of vital capacity.24 Similar results were obtained using cervical magnetic stimulation (CMS).23

The choice of the phrenic nerve stimulation technique is governed by the desire to achieve supramaximality, in that an increase in the size of the stimulus results in no increase in the size of the action potential, implying that all the nerve fibers have been recruited. The importance of the stimulus being supramaximal is that the tension generated by a single stimulus then enjoys a constant relationship, usually around 0.2 in mammalian muscle,62 with the maximal tetanic tension, which is the true strength of the muscle. In humans, a comparable ratio, that of Tw Pdi to maximal voluntary effort Pdi, has been reported between 0.23 63 and 0.24 64 for CMS and 0.24 for BAMPS.24 The surface markings of the phrenic nerve were known to Duchenne,65 and electrical phrenic nerve stimulation was even proposed as a means of emergency ventilatory support in the postwar years.66 Nevertheless, with a few exceptions (see, for example, Dureuil et al67), accurate pressure measurements using bilateral electrical phrenic nerve stimulation (ES) have proved difficult in the ICU. Indeed, even in healthy subjects, the technique is sufficiently imprecise that the lower limit of normal overlaps with diaphragm weakness of both mild and moderate severity.68 The main practical difficulties with ES relate to the need to identify and maintain the precise location of the phrenic nerve with the stimulating electrode, which is, in turn, required to maintain supramaximality. As a consequence, obesity, anatomic deformity, and indwelling venous catheters present clear obstacles. Additionally, the repeated stimuli needed to confirm the position of the stimulating electrode are painful and may lead to Tw potentiation (for more details see Mador et al69 and Wragg et al70).

In 1989, Similowski and colleagues71 successfully applied the technique of magnetic nerve stimulation72 to the phrenic nerves.71 The principle of magnetic nerve stimulation is that electrical energy (up to 3,000 V) from the main supply is stored in a capacitor that is rapidly (in 0.1 ms) discharged by the

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**Figure 3. Nomenclature in the respiratory muscles explained.**

The pressures elicited by ES in a patient with severe COPD are shown (modified from the example in Polkey et al27). For a sniff maneuver, the deflections would still be measured from baseline to peak, and the quantities measured would then be sniff Pdi, sniff Pes, and sniff Pga.
operator through a coil creating a magnetic field. This field, by virtue of Faraday's law, causes current to flow in conducting structures. Thus, provided that the field is sufficiently strong and the phrenic nerves lie within the field, a supramaximal response is obtained. In ambulant patients, the measurement of Tw Pdi following CMS has proven to be of clinical value in the assessment of diaphragm strength and has permitted studies of diaphragm function in patients with advanced respiratory, cardiac, and neurologic disease.11,27,73

CMS requires the placement of the coil behind the cervical spine and may, therefore, be difficult in ICU patients, who are commonly supine and instrumented. Our current practice in the ICU, therefore, is to use BAMPS so that two figure-eight coils are placed anteriorly over the phrenic nerves. This technique may be used bilaterally to assess global diaphragm function or, especially if an iatrogenic etiology is postulated, unilaterally to assess hemidiaphragm function.75,76 Our current practice is to study the patient in the supine or semirecumbent position after a 20-min period of quiet respiration or ventilatory support. The stimulators are linked both to the recording system and to the ETT occlusion valve. Thus, when the operator determines that the patient is at end-expiration (by inspection and from the Pes tracing), a foot pedal is pressed that starts a recording computer and causes a balloon in the occlusion valve to be inflated. After a latent period of 50 to 100 ms, the stimulator is triggered by the recording computer, and at an appropriate interval (ie, approximately 1 s) the balloon valve deflates, allowing respiration to resume. We give stimuli over the surface landmarks of the phrenic nerve in different positions with differing coil orientations. The site of maximum response is marked on the skin, and the process then is repeated on the contralateral side. The actual recording of Tw Pdi is then made from a minimum of five stimuli administered from two stimulators (and two coils) arranged to fire simultaneously in response to the trigger signal from the computer (Fig 4). Because BAMPS at 100% of stimulator output is routinely supramaximal in healthy subjects, we do not, for clinical evaluations, formally demonstrate supramaximality. Nevertheless, if this is desired for academic reasons, we administer a minimum of five series of stimuli at 60%, 70%, 80%, 85%, 95%, and 100% of maximum stimulator output in random order.

Electrophysiology

Electrophysiologic data can be useful to assess the cause and prognosis of a phrenic nerve injury, but they cannot inform the investigator about the pressure-generating properties of the muscle. The simplest measurement is that of phrenic nerve conduction time (PNCT). The PNCT is traditionally measured from surface electrodes in response to unilateral electrical stimulation.77 However, although the PNCT is prolonged in neuropathies that are predominantly demyelinating, it may be preserved in neuropathies that are predominantly axonal despite substantial diaphragm weakness. Thus, in the relevant and frequently studied case of diaphragm dysfunction after cardiac surgery, differing results have been obtained with respect to the PNCT.78–81 Nevertheless, in experienced hands, a complete absence of a surface action potential in response to electrical stimulation of the phrenic nerve can be taken as evidence of iatrogenic injury if there is a plausible clinical history (for example, liver transplantation surgery).82 However, when using the ES technique, it is important that costimulation of the brachial plexus is avoided, otherwise the action potential recorded from surface
electrodes may originate from muscles other than the diaphragm. This problem is compounded if the phrenic nerve is stimulated using a magnetic technique.

More complex neurophysiology of the phrenic nerve requires needle electromyography of the diaphragm and is possible only in highly specialized units, but it may be useful if the results indicate clearly that the etiology is primarily axonal or primarily demyelinating. The former is favored by a normal or slightly prolonged PNCT coupled with a reduced action potential amplitude and the presence of signs of denervation (for example, fibrillation potentials and positive sharp waves). Evidence of a marked prolongation of PNCT or conduction block favors demyelination. In the future, it is possible that reliable data concerning PNCT and compound muscle action potential amplitude may be more widely available using unilateral magnetic stimulation and esophageal electromyography, but, at present, esophageal electrodes are not readily commercially available. Finally, repetitive stimulation combined with the recording of the diaphragm action potential may be useful in the assessment of the neuromuscular junction. In the ICU context, this technique may be useful if the persistence of neuromuscular blockade is suspected.

Quantification of peripheral muscle strength in the ICU, except for simple clinical examination, is uncommon. It is possible to assess the contractile properties of the AP muscle using electrical stimulation of the ulnar nerve in critically ill patients, but not all investigators have found this technique easy to apply. We have recently demonstrated that the Tw tension elicited by supramaximal magnetic stimulation of the ulnar nerve is a reproducible nonvolitional measure of AP strength that can be used in the operating theater and ICU. Similarly, the technique of magnetic stimulation of the femoral nerve to assess quadriceps function can be adapted for use on the ICU. The relevance of peripheral muscle function to respiratory muscle function in the critically ill patient is presently undetermined, but conceptually the identification of peripheral muscle weakness could serve as a (more accessible) marker of respiratory muscle weakness. Furthermore, because these muscles have important functions, therapy aimed at preserving and/or restoring their strength is inherently of interest because it might reduce rehabilitation needs after the patient’s discharge from the ICU.

**Acquired Respiratory Neuromuscular Dysfunction in the ICU**

As previously noted, preexisting neurologic causes of neuromuscular dysfunction are not covered in this review; however, a summary of their causes is shown in Table 2.

**CINMAs**

Although Clarence Olsen reported in 1956 that peripheral nerve lesions could complicate a variety of critical illnesses, systematic studies have been undertaken only relatively recently. The reported studies fall into the following two main groups: those that study unselected ICU patients with prolonged hospital admissions or features of multiorgan dysfunction; and those that study patients with clinical features suggestive of neurologic abnormalities or with specific diagnoses. Reported studies have used a variety of investigational techniques and definitions to report the data. Nev-

**Table 2—Disease Processes Causing Muscle Dysfunction in the ICU**

<table>
<thead>
<tr>
<th>Disease Location</th>
<th>Preexisting Processes</th>
<th>Acquired Processes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve</td>
<td>Motor neuron disease; Guillain-Barré syndrome; iatrogenic (e.g., surgery or central venous access); chronic idiopathic demyelinating polyradiculoneuropathy; toxins (e.g., lead or organophosphates); drugs (e.g., vincristine); porphyria; diphtheria; vasculitis; hereditary tyrosinemia; lymphoma; polynuclitis</td>
<td>Critical illness polynuropathy (axonal or demyelinating); iatrogenic (e.g., surgery or central venous access)</td>
</tr>
<tr>
<td>Neuromuscular junction</td>
<td>Myasthenia gravis; anticholinesterase overdose; antiarrhythmic drugs; Eaton-Lambert syndrome; botulism; envenomation; shellfish poisoning; tick paralysis</td>
<td>Persistence of neuromuscular blockers; antiarrhythmic drugs</td>
</tr>
<tr>
<td>Muscle</td>
<td>Congenital myopathies/dystrophies; polymyositis; electrolyte disorder (e.g., hypokalemia or hypomagnesemia); acid maltase deficiency; circulatory collapse; barium intoxication; endocrine disorder (e.g., hypothyroidism)</td>
<td>Critical illness myopathy; electrolyte disorder (e.g., hypokalemia or hypomagnesemia); steroid myopathy; neuromuscular blockage-induced myopathy</td>
</tr>
</tbody>
</table>
Nevertheless, there is a consensus that among such patients, neurologic abnormalities are common; for example, Spitzer et al.\(^{98}\) concluded that in “difficult-to-wean” patients, 62% had neuromuscular disease sufficiently severe to account for ventilator dependency.

The principal reported abnormalities are the following: axonal neuropathy; demyelinating neuropathy; neuromuscular junction transmission defects; and myopathy. The identification of unsuspected preexisting neurologic disease is a recognized finding in these studies, and this in itself should be considered as a reason to investigate the difficult-to-wean patient. Clinical examination of the ICU patient is difficult, but it should be possible to identify muscle wasting, fasciculation, and the presence or absence of tendon jerks. The preservation of tendon reflexes suggests the absence of abnormalities of the motor nerves but is otherwise nonspecific.\(^{95}\)

The most commonly reported abnormality is an axonal neuropathy.\(^{95,99,107,111,113,114}\) Classically, an axonal neuropathy is characterized by the finding of preserved latencies with diminished action potentials; 2 to 3 weeks after the start of the process, fibrillation potentials and positive sharp waves may be observed.\(^{115}\) However, these features also can occur in myopathic processes,\(^{112}\) and the distinction between axonal neuropathy and myopathy may be difficult.

In demyelinating polyneuropathy, the conduction time is prolonged while the action potential may be reduced or normal in amplitude.\(^{100}\) Some investigators treat this syndrome as Guillain-Barré syndrome (GBS) on the basis that the clinical and electrophysiologic features resemble GBS.\(^{107}\) However, in the largest series, in which 11 cases of GBS were identified,\(^{106}\) only one patient had had weakness before admission to the ICU, and, therefore, in this context GBS could be considered as a complication of critical illness.

Myopathy also can be acquired in the ICU. Most, but not all\(^{98}\) investigators consider it to be less common than axonal neuropathy, although, because of the similarity of their electrophysiologic features, separating the two entities can be difficult. It could be argued that cases identified in the literature as myopathic are in fact axonopathic; however, the argument that myopathy occurs in some patients is firmly supported by histologic and biochemical data\(^{105,112,116}\) as well as by the observation that some patients have muscle that is inexorable even with direct stimulation.\(^{117}\)

Neuromuscular transmission defects also are recognized in the ICU. Occasionally, these can be because of previously undiagnosed myasthenia gravis, especially if the myasthenia has an atypical presentation.\(^{118}\) However, in the ICU, alternative causes are the persistence of neuromuscular blocking agents (NMBAs)\(^{106,119}\) or other drugs.\(^{97}\)

Only a few studies\(^{97,106,107,110,111}\) have investigated the electrophysiology of the respiratory muscles in the ICU, and to our knowledge, no studies have systematically assessed respiratory muscle strength. Zochodne et al.\(^{111}\) studied 17 patients with critical illness polyneuropathy. Only six of these had normal results in phrenic nerve conduction studies, but the nature of the phrenic nerve abnormalities is not described in detail. Witt et al.\(^{97}\) documented a reduction of the compound diaphragm action potential (CDAP) that had a significant correlation with the severity of the peripheral polyneuropathy. Interestingly, a few patients had normal CDAP amplitudes despite peripheral polyneuropathy, and conversely in some cases normal peripheral nerve function was observed despite a reduced CDAP amplitude. Maher et al.\(^{107}\) studied 40 patients in whom an (acquired) neurologic cause for being “difficult-to-wean” was suspected. The prevalence of critical illness polyneuropathy was high (83%), and just under half of these patients had a bilateral phrenic neuropathy; bilateral phrenic neuropathy was not observed in the absence of peripheral polyneuropathy. Other significant diagnoses were unilateral phrenic neuropathies (in one case after surgery) and neuromuscular transmission defects. Zifko et al.\(^{110}\) identified either an abnormal phrenic nerve conduction time or CDAP amplitude in 77% of 62 patients with proven critical illness axonal polyneuropathy. Moreover, patients with a reduced CDAP had a longer requirement for mechanical ventilation than those without (62 vs 55 days, respectively). However, the difference was modest and did not reach statistical significance. Nevertheless, patients with critical illness axonal polyneuropathy involving nonrespiratory nerves are likely to require longer periods of ventilatory support than those without.\(^{100}\) Similarly, such patients are likely to require more prolonged rehabilitation than those without\(^{120}\) or, even, those with myopathy.\(^{106}\)

**Etiologic Factors in CINMAs**

The causes of CINMAs are less well-established (for a fuller discussion see DeJonghe et al\(^{121}\) and Bolton\(^{122}\)); however, multiple organ dysfunction, often but not always sepsis related, does seem to be a recognized risk factor.\(^{97}\) Antibiotics, and in particular aminoglycosides, were exonerated relatively early.\(^{97}\) NMBAs and corticosteroids are two agents that have raised particular concern, although there are clear data that CINMAs can occur without exposure to these drugs.\(^{95,99,105–107}\)
Corticosteroids

Corticosteroids are recognized to cause a proximal myopathy\(^\text{123}\) that also can occur in ICU patients\(^\text{116,124}\) but they are not necessary for the development of critical illness polyneuropathy\(^\text{110}\). Some groups consider the respiratory muscles to be vulnerable to corticosteroids\(^\text{125}\), but we could not confirm this in a study of diaphragm strength in patients with severe Cushing’s syndrome\(^\text{126}\).

NMBAs

One of the first cases of weakness after ICU admission was reported in a patient who had received both NMB and corticosteroid therapy for acute asthma\(^\text{127}\), and the danger of this combination has been subsequently confirmed in larger studies\(^\text{128,129}\). Electrophysiologically, the data suggest that the weakness is because of a combination of axonopathy and myopathy\(^\text{128}\). Moreover, it should be noted that in patients with renal failure, accumulation of the 3-desacyetyl metabolite of vecuronium can occur, leading to a persistent neuromuscular junction transmission defect\(^\text{119,130}\).

Nutrition and Catabolism

Severe malnourishment can result in respiratory muscle weakness\(^\text{131}\), but it is less clear that this is so for patients with more modest decrements in body mass index\(^\text{132}\). Skeletal muscle catabolism may contribute to critical illness myopathy\(^\text{133}\). Critically ill patients exhibit hypermetabolism\(^\text{134}\) with reduced rates of tissue protein synthesis despite nutritional support\(^\text{135}\). Electrolyte disturbance is recognized to impair tension generation in skeletal muscle, and glucose-potassium loading is reported to cause a left shift in the force-frequency curve of the AP muscle in postoperative patients\(^\text{88}\).

Disuse Atrophy

In human limb muscle, immobilization causes a reduction in maximal voluntary contraction force\(^\text{136}\), but a period of >3 weeks is required for changes to occur\(^\text{137}\). However, complete paralysis of the dependent muscle leads to more profound weakness. Anzueto et al\(^\text{138}\) studied three baboons before and after 11 days of complete neuromuscular blockade and observed a 25% reduction in maximal Pdi. Interestingly, in rats, 48 h of heavy sedation was sufficient to produce diaphragm atrophy\(^\text{139}\). Clearly, such experiments would be unethical in humans, but Ayas et al\(^\text{140}\) had the opportunity to study the function of both hemidiaphragms in a phrenic pace-maker-dependent patient in whom the left pacemaker had to be removed because of infection. The patient continued to receive 30 min/d of pacing to the right hemidiaphragm, and this stimulation was sufficient to prevent thinning of the diaphragm, as judged by ultrasound. Thus, available data suggest that atrophy of the respiratory muscles is likely to be a problem only if complete neuromuscular blockade is used for a prolonged period, which is an uncommon clinical scenario.

Fatigue

Fatigue of human skeletal muscle is defined as a loss of force-generating capacity resulting from activity under load that is reversible by rest\(^\text{141}\). A variety of techniques have evolved for the detection of respiratory muscle fatigue including, notably, measurement of the high/low ratio of the power spectrum of the diaphragm electromyogram\(^\text{142}\) and maximum relaxation rate\(^\text{143}\). Data from ICU patients have been produced with both of these techniques\(^\text{144,145}\), but because neither of them strictly addresses the definition of fatigue, the interpretation of these data is problematic. Our view is that they confirm the presence of excessive loading in patients having difficulty weaning from mechanical ventilation, and this is consistent with the observation of abnormal central respiratory drive in similar patients obtained both from needle electromyogram studies of the diaphragm (eg, Maher et al\(^\text{107}\)) and Zifko et al\(^\text{110}\) and of increased tracheal occlusion pressure\(^\text{146}\).

The type of fatigue that is of greatest potential relevance to clinical practice is low-frequency fatigue (LFF)\(^\text{16}\) in that activity under load results in a loss of force generated in response to low stimulation frequencies (eg, 10 to 20 Hz). LFF is of interest both because these are the typical firing frequencies of respiratory muscle motor units in humans\(^\text{147,148}\) but also because, unlike other forms of fatigue, the effects may last \(-\)24 h\(^\text{18,92,149}\). Ideally, the demonstration of LFF requires the construction of the force-frequency curve. However, although it is possible to construct force-frequency relationships of the diaphragm in highly motivated healthy subjects\(^\text{56}\), using tetanic electrical stimulation, the technique is impracticable in patients (although interest remains in deducing the force-frequency curve by paired stimulation\(^\text{24,150,151}\)). Instead, the pressure elicited by a single supramaximal stimulus (ie, the Tw Pdi) is used as a substitute. Using this technique, diaphragmatic LFF has been demonstrated in healthy subjects in the laboratory after resistive loading\(^\text{149}\), maximal voluntary ventilation\(^\text{152,153}\) and whole-body exercise\(^\text{154}\) and the technique also may be adapted for the abdominal muscles\(^\text{155}\). However, few studies
have investigated the presence of fatigue in clinical situations using phrenic nerve stimulation techniques, and the two studies that have been reported, failed to demonstrate LFF in COPD patients. The application of magnetic stimulation allows the study of patients with critical illness and, although this question is the subject of current research by a number of groups (including our own), to our knowledge, no data have yet been reported. Trials of spontaneous ventilation are currently considered the optimal method of weaning from mechanical ventilation, and, because the possibility of respiratory muscle fatigue after such trials cannot be excluded, it seems logical to propose that such trials not be conducted more frequently than daily.

**CONCLUSION**

Once cardiac and pulmonary causes have been excluded, prolonged ventilator dependency is most likely to be due to undiagnosed acquired neuromuscular disease. The use of neuromuscular blocking drugs and corticosteroids should be kept to the minimum required for the management of the primary condition. Hitherto, demonstrating respiratory muscle dysfunction in critically ill patients required specialist neurophysiologic investigation, but the application of the recently developed technique of magnetic stimulation of the phrenic nerves should allow most specialist pulmonologists and intensivists to confirm or refute this diagnosis when necessary. We recommend that respiratory muscle strength be measured in patients with > 7 days of ventilator dependency in whom a cardiac or respiratory cause is not identified. If respiratory muscle weakness is identified, electrophysiological assessment by a specialist is indicated to exclude the treatable conditions of neuromuscular transmission defect and GBS. Furthermore, we predict that the application of such techniques in academic studies will allow further understanding of the impact of CINMAs on the respiratory muscles. Similarly, by determining the importance, or otherwise, of low-frequency respiratory muscle fatigue in critically ill patients, it is hoped that more evidence-based weaning strategies can be studied in future trials.

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