Electrophysiologic techniques in critical illness-associated weakness

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Abstract

Neuromuscular disorders are increasingly recognized in the critically ill but conventional electrodiagnostic techniques often provide non-specific results or are hampered by local conditions that prevent adequate disease classification. Muscle fiber inexcitability is a common phenomenon in critical illness myopathy possibly secondary to disordered sodium channel fast inactivation and associated with loss of myosin staining. Direct muscle stimulation techniques, measuring evoked response amplitudes and comparison of nerve and muscle stimulated responses, are recognized methods of demonstrating this phenomenon. Other measures studied in this population include increased compound motor action potential duration, motor unit number estimates and mean step area of individual motor unit potentials during motor unit number estimate studies. An electrophysiologic approach to the study of patients with critical illness associated weakness is proposed.

Keywords: Critical illness myopathy; Direct muscle stimulation; Muscle fiber inexcitability; Acute quadriplegic myopathy; Motor unit number estimation

1. Introduction

Neuromuscular disorders in the critically ill (CI) are recognized with increasing frequency. Muscle wasting and weakness is common in the CI. Because electrophysiologic testing of patients in the intensive care unit (ICU) is often hampered by necessary life support equipment and other forms of interference, the amount of diagnostic testing should be limited to those techniques best suited to reveal the cause. Although muscle biopsy may show characteristic selective thick filament loss, less specific type II fiber atrophy, or necrotizing myopathy, histologic examination is not a practical screening tool. The tests best suited to distinguish between critical illness myopathy (CIM) and critical illness polyneuropathy (CIP) are disputed.

Conventional nerve conduction studies (NCS) and electromyography (EMG) are commonly used to classify these conditions, but they often provide non-specific findings that fail to distinguish myopathic from neurogenic causes of weakness. Both CIP and CIM frequently demonstrate reduced compound muscle action potential (CMAP) amplitudes, and abnormal spontaneous activity is common in both, often presumptively attributed to an underlying neurogenic process. Voluntary motor unit (MU) analysis is often problematic because data may be markedly limited by severe weakness, impaired voluntary effort or clouded mental status. Sensory nerve conduction studies have been the ultimate differentiating feature but local edema, other electronic devices, lines and monitors, and other limitations frequently hamper reliable sensory recordings in the ICU. Moreover, the absence of a sensory nerve action potential (SNAP) may be potentially caused by sodium channel dysfunction and is not necessarily caused by peripheral nerve degeneration or CIP. According to Cunningham et al., the resting transmembrane potential difference of skeletal muscle in severely ill hospitalized patients is about 23 mV lower than in normal subjects ($-66.3\pm9.0$ mV vs. $-89\pm3.8$ mV) due to increased intracellular sodium concentrations in severely ill patients compared to normal subjects probably caused by a generalized cellular abnormality – a common quality of serious illness, and probably the first evidence of a sodium channelopathy [1].

Some 25 years later, Rich et al. proposed CIM to be a disorder of skeletal muscle in which weakness is due to
failure of muscle fibers to generate action potentials [2,3]. The technique of direct muscle stimulation was employed to support, in affected patients, a loss of muscle fiber excitability separate from loss of function from neurogenic denervation. A later animal model suggested that impaired sodium channel inactivation, especially sodium channel fast inactivation, is an important contributory factor [4,5]. Serum fractions from CIM patients also affect membrane excitability and intracellular calcium release [6].

2. Direct muscle stimulation

Before meaningful conclusions can be drawn about clinical outcome or future attempts at intervention examined, proper classification of the underlying causes of weakness is necessary. To improve diagnostic yield and overcome the pitfalls mentioned, measurement of muscle fiber excitability using the direct muscle stimulation (DMS) techniques suggested by Rich et al. has been examined [2]. Stimulation of muscle fibers and recording potentials distal to the endplate zone is a well-established technique to circumvent the neuromuscular junction for measurement of muscle fiber excitability and the rate of conduction along muscle fibers. Studies in earlier eras employed single-fiber EMG electrodes in order to precisely determine single muscle fiber conduction velocity. The technique has been adapted in recent years to assess muscle fiber excitability through the use of surface, subdermal and in some cases conventional concentric and monopolar needle electrodes for stimulation and recording. For our method, the muscle is stimulated just proximal to the tendon insertion using a conventional surface electrode; others have used a monopolar needle electrode [7]. If a muscle twitch is visible, a subdermal or concentric needle electrode is placed over its center, 30–40 mm proximal to the site of stimulation. When the recording electrodes are in the same montage, the relevant peripheral nerve is also stimulated. The ratio of the nerve evoked (nCMAP) response amplitude to the muscle evoked (mCMAP) response amplitude is calculated. When this ratio is >0.5, impaired muscle membrane excitability is suggested [3]. Evoked response amplitude and muscle fiber conduction velocity are also measured. Studies have shown that CMAP amplitudes evoked by DMS below 1.0 or 3.0 mV for subdermal or concentric needle electrodes recording, respectively support impaired muscle membrane excitability [7]. Acute neurogenic processes in contrast have shown robust DMS responses but reduced or absent nerve stimulated responses [3,8]. Normal muscles, however, show similar mCMAP and nCMAP amplitudes suggesting that the ratio alone is an insufficient marker in isolation. One report found the expected pattern of preserved muscle fiber excitability in acute neurogenic conditions, such as axonal Guillain-Barré syndrome and nerve injury, but impaired DMS amplitude in more chronic severe neurogenic states [8]. These studies suggest that the expected pattern of preserved muscle excitability despite an impaired nerve stimulated response is best seen in acute stages, prior to the development of muscular atrophy.

3. Other techniques

Other electrophysiologic measures to separate myopathy from neuropathy have been suggested. An interesting observation was made in a case study presented in 1997 at the Massachusetts General Hospital’s “Weekly Clinico-pathological Exercises” [9]. The patient in question suffered from chronic obstructive pulmonary disease and was hospitalized for respiratory failure and longstanding history of alcoholic abuse. After a 1-month stay in the hospital, he became tetraplegic with absent deep tendon reflexes. Nerve conduction studies showed low amplitude CMAPs and marked prolongation of the muscle responses without signs of desynchronization. Motor nerve conduction velocities and F-wave responses were normal as were all sensory evoked responses. EMG revealed no spontaneous activity. Despite profound weakness, a full recruitment pattern was readily obtained. The distal CMAP duration on the 34th hospital day was 9.4 ms and 10.0 ms for the abductor pollicis brevis and adductor digitii minimi, respectively, and increased to 12.7 and 14.0 ms a month or so later. When muscle strength improved, amplitudes returned to normal followed by gradual correction of the dispersion of the CMAPs. The clinical, laboratory and electrophysiological features of the case were compatible with CIM-associated myosin deficiency. Serum creatine kinase was increased at onset but reached normal values within the 2nd week of disease. Biopsy of the right deltoid muscle showed marked diffuse fiber atrophy with numerous small, angulated fibers. Electron microscopy revealed a striking loss of thick myosin filaments compatible with critical illness myopathy. The

Table 1

<table>
<thead>
<tr>
<th>CMAP measures (means ± S.E.M.) from patients with critical illness myopathy</th>
<th>Park et al. [10]</th>
<th>Trojaborg et al. [7]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (ms)</td>
<td>Amplitude (mV)</td>
<td>No</td>
</tr>
<tr>
<td>Median</td>
<td>12.4±1.8</td>
<td>2.2±0.8</td>
</tr>
<tr>
<td>Ulnar</td>
<td>13.5±1.6</td>
<td>1.2±0.4</td>
</tr>
<tr>
<td>Peroneal</td>
<td>18.1±1.7</td>
<td>0.8±0.1</td>
</tr>
<tr>
<td>Tibial</td>
<td>13.4±2.2</td>
<td>2.9±1.1</td>
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dispersion of the CMAP could not be explained by the histological findings but is likely related to mechanisms affecting excitable membranes either in the distal part of the motor axons or the sarcolemma as no evidence of demyelination of intramuscular motor axons was noted. It was suggested that dispersion could be caused by slowing of muscle fiber conduction velocity as a result of impairment or blockade of certain voltage gated ion channels.

Park et al. reviewed 9 cases examined in the ICU between 1999 and 2003 with possible CIM diagnosed by electrophysiological evaluations [10]. The CMAPs evoked by stimulation of the median, ulnar, peroneal and tibial nerves showed markedly reduced amplitude and increased CMAP negative phase duration, the highest value being more than 300% of the upper limit of normal; however, the waveforms remained synchronous and smooth. Moreover, CMAP duration was not significantly different between proximal and distal stimulation sites. The authors concluded that determination of the CMAP duration is a quick and simple diagnostic bedside test preferable to other electrophysiological tests to distinguish CIM from CIP [10].

In an attempt to examine whether CMAP duration could differentiate myopathy from neuropathy in the ICU, we measured median, ulnar, peroneal and tibial CMAP’s in 22 cases of CIM verified by EMG and biopsy [7] and compared the results to 19 patients with an axonal form of diabetic neuropathy. Because mean values of duration and distal amplitudes did not differ significantly between the 2 groups, all values were pooled. The mean duration and amplitude were 8.9 ± 0.04 ms and 2.8 ± 0.03 mV, respectively, thus not supporting the increased values reported in the case history mentioned (Table 1).

Estimation of the number of functioning motor units (MUNE) has also been examined in this population. Motor unit numbers should be normal in myopathy but reduced in neurogenic conditions. In general, MUNE techniques are time-consuming and difficult to apply in an ICU setting. Another technique to discriminate myopathy from neuropathy is the calculation of the average value of the mean step area of individual motor unit potentials (MUPs) when using motor unit number estimate techniques (MUNE). Baslo et al. found an average value of mean step area of 2.46 ± 0.88 mV ms in normal control subjects compared to 36 ± 1.94 mV ms in patients with motor neuronopathy and 1.06 ± 0.61 in patients with myopathy. In five patients with histologically verified myopathy with loss of thick myosin filaments, the mean step area was 0.34 ± 0.07 mV ms [11]. In addition, motor unit number estimates were also within normal limits in this study and an earlier series [7,11]. Although the number of cases examined in this way is few, it is a promising but not commonly used test in the ICU, likely because it is difficult and rather time consuming to perform and analyze. DMS has so far been considered the best electrophysiologic test to separate CIM from CIP in the ICU [12].

4. A diagnostic strategy

The following strategy for the electrophysiologic evaluation of weakness in the ICU is proposed:

1) Determination of CMAP amplitude and duration of small hand and foot muscles as a measure of force and atrophy;
2) Antidromic recording of the radial sensory nerve action potential (because this site may be less affected by edema and other technical limitations);
3) EMG of proximal and distal muscles of the upper and lower extremities;
4) Direct muscle stimulation (DMS);
5) Quantitative motor unit potential analysis if sufficient EMG potentials are available for analysis.

References