

Emerging Clinical Applications of Neurophysiological Assessment of Sarcolemmal Excitability

Muscle disorders are regularly encountered by neurologists and clinical neurophysiologists. Nerve conduction studies are either normal or reveal reduced compound muscle action potential (CMAP) amplitudes. Needle electromyography (EMG) may reveal spontaneous activity (fibrillations or positive sharp waves), myopathic motor units and abnormal recruitment patterns. Structural muscle changes (variation in fibre size and a predominance of smaller fibres) contribute to the 'myopathic' EMG. Some muscle disorders however are due to muscle fibre membrane ion channel dysfunction. Increased muscle fibre membrane excitability may result in spontaneous discharges, clinically manifesting as myotonia or stiffness. Reduced excitability may cause slowing or failure of action potential propagation, which may manifest as weakness or paralysis. In a similar way to nerve excitability studies, the pathophysiological consequences of ion channel mutations on muscle membrane function can be assessed using neurophysiological techniques, complementing advancing knowledge of the genetic and molecular defects and of clinical phenotypes.

For muscle contraction to occur, conduction of action potentials along the muscle fibre membrane is dependent upon normal membrane excitability. Depolarisation is mediated by the Na_v1.4 Na⁺ channel, product of the *SCN4A* gene. Calcium ions are subsequently released from the sarcoplasmic reticulum mediating excitation-contraction coupling. Chloride channels (encoded by *CLCN1*), which have high conductance near the resting membrane potential, stabilise it in the resting and post-excitation state.

Assessments of CMAP morphology, muscle fibre conduction velocity (MFCV) and short and long exercise tests can all be helpful in assessing membrane function. Action potential propagation velocity along the muscle fibre membrane (MFCV) can be estimated by cross-correlation of surface recorded EMG¹ or invasive methods.²⁻⁴

In myotonias, exercise can trigger, relieve or aggravate symptoms, so it can be used as a neurophysiological functional test, to aid diagnosis. The short exercise test, first described by Streib et al is useful in investigating myotonic disorders.⁵ Repeated brief exercises are followed by rest and serial supramaximal CMAP recordings. The long exercise test, described by McManis et al is useful for the assessment of suspected periodic paralysis.⁶

To illustrate the potential utility of EMG techniques the following will describe recent work relating to the non-dystrophic myotonias and critical illness myopathy, where these investigations have been used.

Myotonias

Muscle fibre hyperexcitability is the fundamental abnormality in myotonia, resulting in spontaneous trains of action potentials, which with contraction coupling results in delayed relaxation. Myotonic discharges arise from single muscle fibres. They show rapid firing, waxing and

waning of frequency and amplitude, and may be facilitated by mechanical stimuli. However, myotonic discharges are not diagnostically distinctive according to cause. In the absence of prominent clinical myotonia, electrical myotonia is observed in, amongst others, acid maltase deficiency, congenital myopathies, hypothyroidism and polymyositis. These conditions may also possess motor unit and recruitment abnormalities on EMG.

Routine assessment of myotonia relies upon needle EMG revealing myotonic discharges. Neurophysiological provocative tests including repetitive nerve stimulation,⁷ short and long exercise tests, can help distinguish the main phenotypes.

Broadly divided into two groups, variants of myotonia congenita (MC) are caused by dominant or recessive mutations of the chloride channel gene (*CLCN1*). Myotonia increases after periods of rest and declines with repetition of exercise (warm up phenomenon). Mutations of the alpha subunit of the voltage gated skeletal muscle sodium channel gene (*SCN4A*) have been found to cause paramyotonia congenita (PC), where myotonia conversely is induced by exercise or cold. Clinical history and examination is frequently enough to be able to guide genetic testing, however it is sometimes unreliable or the phenotype unclear, for example, some *SCN4A* mutations produce myotonia without an increase after exercise, mimicking MC.⁸

Recent studies have addressed the utility of the short and long exercise tests in the non-dystrophic myotonias and have found them to be helpful in supporting the diagnosis and guiding genetic testing. Fournier et al studied patients with identified ion channel mutations, using a modified form of the short exercise test.⁹ Instead of the originally described 10 minute rest period between tests, they used three brief exercise periods separated by only 1 minute each. In patients with myotonia congenita, Fournier, like Strieb previously, noted an initial decline in CMAP amplitude following exercise which gradually improved with further exercise, similar to the clinically recognised warm-up effect. Based on the findings they defined five electrophysiological groups, which distinguished between sodium, chloride and calcium channel mutations and also between subgroups of sodium channelopathies. The first three groups related to myotonic syndromes, which were distinguishable using repeated short exercise tests. The reported sensitivity of the repeated short exercise test was about 85%. Further work studying 54 patients with myotonia identified sodium or chloride channel mutations, describing increased sensitivity (approaching 90-100%) of the short exercise test when combined with muscle cooling.¹⁰

The patterns recorded correlate with the clinical symptoms. Those with PC due to the most common sodium channel mutations displayed a pattern of post exercise decreasing CMAPs, aggravated by repetition. Cold augments this decline in excitability. The common mutations impair inactivation of the channels and an increase in the sustained current, causing increased membrane excitability and myotonia or reduced excitability with paralysis,



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The pathophysiological and clinical consequences of ion channel dysfunction can be assessed using neurophysiological techniques

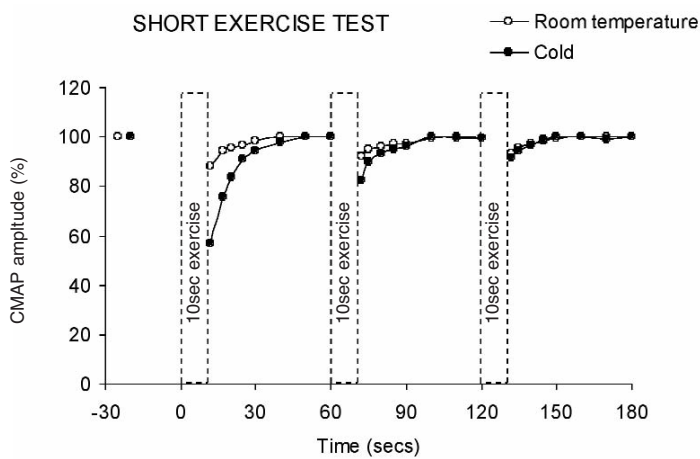


Figure 1: Example of Short exercise test result with the effect of cooling in a MC patient suggestive of a recessive Chloride channel mutation.

depending upon the degree of depolarisation.¹¹⁻¹³ Cooling induces membrane depolarisation by slowing ion channel kinetics; hence in PC, cold has a depolarising effect, causing myotonia and then inexcitability.^{14,15} At room temperature almost all MC patients with recessive chloride channel mutations displayed a transient decrease in the CMAP when the short exercise test was performed after rest, which improves after short exercise test repetition, akin to the warm-up phenomenon. However, those with dominant mutations generally (86%) did not show this reduction following exercise under normal conditions but the majority (75%) did once there had been exposure to cold.

Fournier et al suggested that EMG can guide specific ion channel gene testing and that combining exercise tests with cold exposure improves the sensitivity. Prospective studies testing this hypothesis should be performed. Studies should also look at reproducibility and at the usefulness of such testing in patients with these mutations but milder phenotypes.

Critical illness myopathy (CIM)

In contrast to hyperexcitability causing myotonia, muscle inexcitability has been demonstrated in critical illness myopathy.^{16,17} Differentiating between a myopathy and neuropathy can be challenging in the intensive care unit. The differential diagnosis in ICU also includes Guillain Barré syndrome and myasthenia gravis for example. In a series of 92 patients with neuromuscular disorders acquired in the ICU, a myopathy consistent with CIM was three times as common as axonal polyneuropathy and is increasingly recognised.¹⁸ Careful neurophysiological examination can differentiate these conditions. The ratio of the CMAPs recorded following direct muscle stimulation and motor nerve stimulation has been used to distinguish myopathy and neuropathy in ICU patients, this is however only semi-quantitative and has potential disadvantages.^{17,19} Early in CIM paralysis there are fibrillation potentials and positive sharp waves on EMG. Recruitment and motor unit potentials appear myopathic. Subsequently the muscle becomes inexcitable. Myosin loss demonstrated on biopsy cannot explain muscle fibre membrane inexcitability and its loss lags behind the development of weakness.^{20,21}

We recently demonstrated acquired dysfunction at the level of the muscle fibre membrane in critical illness myopathy, akin to that seen in some inherited channelopathies.⁴ We found that in 90% of CIM patients, compared to controls, the CMAP duration recorded from either abductor hallucis (AH) or abductor pollicis brevis (APB) was significantly prolonged, exceeding the control mean + 2 SD in either or both the median or tibial responses. The morphology of the abnormal CMAP is also distinctive, being smoothly contoured and the positive phase is often replaced by a long negative phase (Figure 2). Other pathologies can cause CMAP duration prolongation e.g. demyelinating neuropathies; however the morphology is then typically irregularly dispersed (desynchronised) and associated with other nerve conduction abnormalities.

To further understand the underlying pathophysiology of this phenomenon we looked at MFCV, using an invasive technique. It was significantly slowed in CIM, the mean being 2.3m/s compared to 4.0m/s in

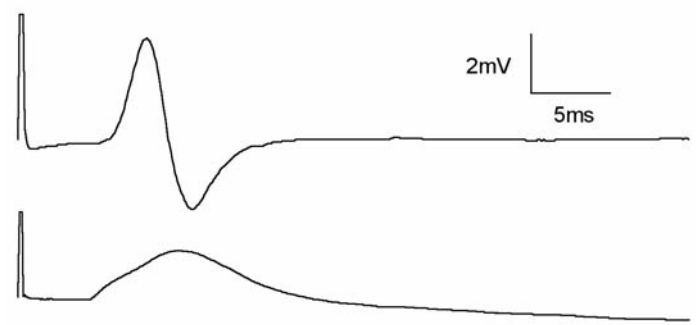


Figure 2: CMAPs recorded from a normal control (above) and from a patient with CIM demonstrating 'synchronised dispersion', which is the combined result of slowing of muscle fibre conduction velocities and widening of its range. Note the absence of the positive phase and the 'long tail'.

controls. Some muscles and fibres were inexcitable or indirectly demonstrated muscle fibre conduction block. An inverse relationship between MFCV and CMAP duration was found, which was also proportional to the clinical severity. Hence the smooth CMAP contour probably reflects slowed and dispersed but synchronous depolarisation of muscle fibres. A paired stimulation technique was used to assess the refractory period of individual muscle fibres in vivo, which suggested a longer refractory period, CIM mean 4.7ms compared to controls mean of 2.5ms. CK is almost always normal or only mildly elevated in CIM.^{4,19} In fact CK is disproportionately low for the degree of weakness, supporting the notion that weakness is due to dysfunction rather than structural change at onset. In the critically ill, the resting membrane potential may become depolarised due to generalised cellular dysfunction²² or other factors.²³ In keeping with this hypothesis, in an animal model of CIM, inactivation of voltage dependant sodium channels has been demonstrated, which results in reduced sodium currents.²⁴⁻²⁶

Hypokalaemic periodic paralysis (HPP) type 2, due to SCNA4 mutations, results in sodium channel dysfunction. In HPP, MFCV is reduced interictally and further declines during attacks of paralysis.^{27,28} Early on during paralytic episodes fibrillation potentials are present indicating depolarised membranes.²⁹ Paralysis arises following membrane depolarisation triggered sodium channel inactivation, rendering the muscle inexcitable.⁸ In CIM it is presumed that a similar depolarising shift in membrane potential, due to either a generalised cellular dysfunction or the presence of circulating factor or factors, contributes to sodium channel dysfunction and a similar dynamic pattern of electrophysiology. The neurophysiological findings in CIM and HPP share common themes. The parallels suggest a similar pathophysiology at the membrane level, although in CIM this is precipitated at least by a degree of acquired channel dysfunction. Functional polymorphisms in human cardiac muscle ion channels can mediate arrhythmia susceptibility,^{30,31} and it would therefore be interesting to look for these Na⁺ channel polymorphisms in CIM patients. The parallels help our understanding of these conditions and might afford therapeutic possibilities.

Work on the basic pathophysiological mechanisms, has improved our understanding of critical illness myopathy and may also help its recognition, diagnosis and monitoring. In addition to fibrillations and a myopathic EMG, the synchronous dispersion of the prolonged CMAP is characteristic. Weaker patients have lower MFCV or inexcitable fibres on direct muscle stimulation and longer CMAP durations.

Conclusion

Limited studies have been performed in both CIM and in the myotonias. Further work should address reliability and reproducibility, and should investigate the interplay between genetics, neurophysiology and phenotypes. Understanding the precipitants of dysfunction also requires clarification. Our understanding and ability to accurately diagnose both common and rare muscle disorders related to sarcolemmal hyperexcitability or hypoexcitability is improving. The neurophysiological assessment can play an important role in this respect, providing accurate and timely diagnosis in the ICU and by directing genetic testing, which is more expensive and time consuming.

References

- Arendt-Nielsen L, Mills K. *Muscle fibre conduction velocity, mean power frequency, mean EMG voltage and force during submaximal fatiguing contractions of human quadriceps*. Eur J Appl Physiol 1998;58:20-25.
- Stålberg E, Trontelj J. *Single fibre electromyography. Studies in healthy and diseased muscle, 2nd Edn*. New York, Raven Press. 1994.
- Troni W, Cantello R, Rainero I. *Conduction velocity along human muscle fibers in situ*. Neurology. 1983;33(11):1453-9.
- Allen D, Arunachalam R, Mills K. *Critical illness myopathy: Further evidence from muscle-fiber excitability studies of an acquired channelopathy*. Muscle and Nerve 2008;37(1):14-22.
- Streib E, Sun S, Yarkowski T. *Transient paresis in myotonic syndromes: a simplified electrophysiological approach*. Muscle Nerve 1982;5:719-23.
- McManis P, Lambert E, Daube J. *The exercise test in periodic paralysis*. Muscle Nerve 1986;9:704-10.
- Aminoff M, Layzer R, Satya-Murti S, Faden A. *The declining electrical response of muscle to repetitive nerve stimulation in myotonia*. Neurology 1977;27:812-16.
- Lehmann-Horn F, Jurkat-Rott K. *Voltage gated ion channels and hereditary disease*. Physiol Rev 1999;79:1317-2.
- Fournier E, Arzel M, Sternberg D, Vicart S, Laforet P, Eymard B, Willer J-C, Tabti N, Fontaine B. *Electromyography guides toward subgroups of mutations in muscle channelopathies*. Ann Neurol 2004;56:650-61.
- Fournier E, Viala K, Gervais H, Sternberg D, Arzel-Hezode M, Laforet P, Eymard B, Tabti N, Willer J-C, Vial C, Fontaine B. *Cold extends electromyography distinction between ion channel mutations causing myotonia*. Ann Neurol 2006;60:356-65.
- Hayward L, Brown R, Cannon S. *Inactivation defects caused by myotonia-associated mutations in the sodium channel III-IV linker*. J Gen Physiol 1996;107:559-76.
- Lehmann-Horn F, Rudel R. *Molecular pathophysiology of voltage gated ion channels*. Rev Physiol Biochem Pharmacol 1996;128:195-268.
- Cannon S, Brown R, Corey D. *Theoretical reconstruction of myotonia and paralysis caused by incomplete inactivation of sodium channels*. Biophys J 1993;65:270-88.
- Ruff R. *Effects of temperature on slow and fast inactivation of rat skeletal muscle Na (+) channels*. Am J Physiol 1999;277:937-47.
- Mohammadi B, Mitrovic N, Lehmann-Horn F et al. *Mechanisms of cold sensitivity of paramyotonia congenital mutation R1448H and overlap syndrome mutation M1360V*. J Physiol 2003;547:691-8.
- Rich MM, Teener JW, Raps EC, Schotland DL, Bird SJ. *Muscle is electrically inexcitable in acute quadriplegic myopathy*. Neurology. 1996;46(3):731-6.
- Rich MM, Bird SJ, Raps EC, McCluskey LE, Teener JW. *Direct muscle stimulation in acute quadriplegic myopathy*. Muscle Nerve. 1997;20(6):665-73.
- Lacomis D, Petrella JT, Giuliani MJ. *Causes of neuromuscular weakness in the intensive care unit: a study of ninety-two patients*. Muscle Nerve. 1998;21(5):610-7.
- Lefaucheur JP, Nordine T, Rodriguez P, Brochard L. *Origin of ICU acquired paresis determined by direct muscle stimulation*. J Neurol Neurosurg Psychiatry. 2006;77(4):500-6.
- Showalter CJ, Engel AG. *Acute quadriplegic myopathy: analysis of myosin isoforms and evidence for calpain-mediated proteolysis*. Muscle Nerve. 1997;20(3):316-22.
- Zifko UA, Zipko HT, Bolton CF. *Clinical and electrophysiological findings in critical illness polyneuropathy*. J Neurol Sci. 1998;159(2):186-93.
- Cunningham JN Jr, Carter NW, Rector FC Jr, Seldin DW. *Resting transmembrane potential difference of skeletal muscle in normal subjects and severely ill patients*. J Clin Invest. 1971;50(1):49-59.
- Friedrich O, Hund E, Weber C, Hacke W, Fink RH. *Critical illness myopathy serum fractions affect membrane excitability and intracellular calcium release in mammalian skeletal muscle*. J Neurol. 2004;251(1):53-65.
- Rich MM, Pinter MJ, Kraner SD, Barchi RL. *Loss of electrical excitability in an animal model of acute quadriplegic myopathy*. Ann Neurol. 1998;43(2):171-9.
- Rich MM, Pinter MJ. *Sodium channel inactivation in an animal model of acute quadriplegic myopathy*. Ann Neurol. 2001;50(1):26-33.
- Rich MM, Pinter MJ. *Crucial role of sodium channel fast inactivation in muscle fibre inexcitability in a rat model of critical illness myopathy*. J Physiol. 2003;547(Pt2):555-66.
- Troni W, Doriguzzi C, Mongini T. *Interictal conduction slowing in muscle fibers in hypokalaemic periodic paralysis*. Neurology. 1983;33(11):1522-5.
- Links TP, van der Hoeven JH, Zwarts MJ. *Surface EMG and muscle fibre conduction during attacks of hypokalaemic periodic paralysis*. J Neurol Neurosurg Psychiatry. 1994;57(5):632-4.
- Gordon AM, Green JR, Lagunoff D. *Studies on a patient with Hypokalaemic familial periodic paralysis*. Am J Med. 1970;48(2):185-95.
- Kubota T et al. *Evidence for a single nucleotide polymorphism in the KCNQ1 potassium channel that underlies susceptibility to life threatening arrhythmias*. J Cardiovasc Electrophysiol 2001;12:1223-9.
- Viswanathan P, Benson D, Balsler J. *A common SCN5A polymorphism modulates the biophysical effects of an SCN5A mutation*. J Clin Invest 2003;111:341-6.

National clinical guideline for stroke Third edition

Prepared by the Royal College of Physicians Intercollegiate Stroke Working Party co-chaired by Professor Derick Wade and Dr Tony Rudd

The third edition of these world-renowned stroke guidelines provides the reader with the most comprehensive coverage of stroke care to date, encompassing the whole of the stroke pathway from acute care through to longer-term rehabilitation and secondary prevention. It informs health professionals about what should be delivered to stroke patients and how this should be organised, with the aim of improving the

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