Clinical Neurophysiology Practice 9 (2024) 176–200

Contents lists available at ScienceDirect

Clinical Neurophysiology Practice

journal homepage: www.elsevier.com/locate/cnp

Review article

Revisiting the compound muscle action potential (CMAP)

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ARTICLE INFO

Article history:
Received 7 December 2023
Received in revised form 15 April 2024
Accepted 21 April 2024
Available online 08 May 2024

Keywords:
Compound muscle action potential
Motor nerve conductions
Surface recording electrodes
MUNE

ABSTRACT

The compound muscle action potential (CMAP) is among the first recorded waveforms in clinical neurography and one of the most common in clinical use. It is derived from the summated muscle fiber action potentials recorded from a surface electrode overlying the studied muscle following stimulation of the relevant motor nerve fibres innervating the muscle. Surface recorded motor unit potentials (SMUPs) are the fundamental units comprising the CMAP. Because it is considered a basic, if not banal signal, what it represents is often underappreciated. In this review we discuss current concepts in the anatomy and physiology of the CMAP. These have evolved with advances in instrumentation and digitization of signals, affecting its quantitation and measurement.

It is important to understand the basic technical and biological factors influencing the CMAP. If these influences are not recognized, then a suboptimal recording may result. The object is to obtain a high quality CMAP recording that is reproducible, whether the study is done for clinical or research purposes.

The initial sections cover the relevant CMAP anatomy and physiology, followed by how these principles are applied to CMAP changes in neuromuscular disorders. The concluding section is a brief overview of CMAP research where advances in recording systems and computer-based analysis programs have opened new research applications. One such example is motor unit number estimation (MUNE) that is now being used as a surrogate marker in monitoring chronic neurogenic processes such as motor neuron diseases.

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Contents

Abbreviations: AANEM, American Association of Neuromuscular and Electrodiagnostic Medicine; ADM, abductor digiti minimi manus; AP, action potential; APB, abductor pollicis brevis; AH, abductor hallucis; CI, critical illness; CMAP, Compound Muscle Action Potential; CMP, Compound Muscle Potential; CV, Conduction Velocity; CoV, Coefficient of Variation; E0, Electrode 0, synonymous with "Ground" Electrode; E1, Electrode 1, synonymous with "active" or "G1" electrode; E2, Electrode 2, synonymous with "reference" or "G2" electrode; ENMG, electroneuromyography (includes nerve conduction studies and electromyography; G1, Grid 1 synonymous with "active" or "E1" electrode; G2, Grid 2 synonymous with "reference" or "E2" electrode; ISI, Inter-stimulus interval; MF, muscle fibers; MNCS, motor nerve conduction study; Ms, M satellite or CMAP satellite; MU, motor unit(s); MUNE, motor unit number estimation; MUNIX, motor unit number index; MUSIX, motor unit size index; NI, Neurophysiological Index; PMP, premotor potential; RV, reference value; SIP, surface interference pattern; SMUP, surface-recorded motor unit potential; TA, tibialis anterior.

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https://doi.org/10.1016/j.cnp.2024.04.002
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1. Introduction

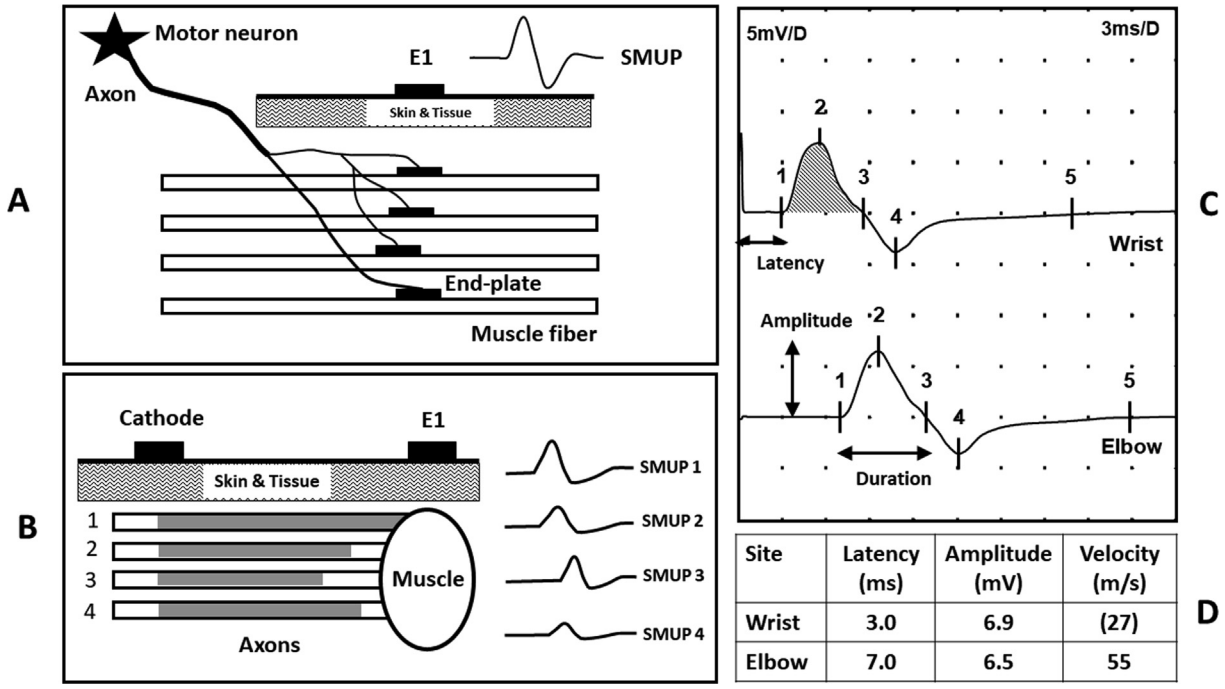
This review follows our previous work and interest in Motor Unit Number Estimation (MUNE) which was the subject of a previous review (de Carvalho et al., 2018). The quintessence of MUNE is the compound muscle action potential (CMAP) or "M wave" recorded from a muscle as a result of motor nerve stimulation. It is the fundamental signal in motor nerve conduction and related studies (e.g., F waves, H reflex, repetitive motor nerve stimulation, etc.). It is thought to be a banal, simple waveform, often taken for granted. As instrumentation has progressed, the CMAP is now being appreciated as a much more nuanced signal with potential for advanced applications in research (section 11).

In the earliest textbooks (Downie, 1964; Downie, 1974; Norris, 1963), the "M wave" (or CMAP) did not receive much attention. There is discussion of terminal latency and "conduction rate" (i.e., conduction velocity) along with normative data for velocity. While the "muscle action potential" is mentioned, no parameters or values are provided, most likely due to the use of needle electrodes in recordings. Leblanc (2023) has recently described Herbert Jasper's contributions, while working in Paris 1931–1933, to the early development of clinical EMG. If we consider the CMAP as the holy grail, the earliest textbooks described estimates of how "far" it was ("latency") and how "long it might take to get there" ("conduction velocity"), but ironically nothing about the object of the quest (recording) itself. In the current practice of electroneuromyography (ENMG) (Stålberg et al., 2019), the term CMAP with its associated measurements has become well-established. Published reference data are available regarding the minimum accepted amplitudes and maximum latencies in several nerve-muscle systems although it is essential that each laboratory develops their own or that they confirm the validity of their data with published data from other labs (see section 9).

Given the importance of this signal in standard ENMG practice, and in advanced techniques such as MUNE, it is appropriate to review the anatomic aspects and physiological composition of the CMAP and how it is affected by technical and biological factors. With advances in digital recordings, some of our traditional concepts of the CMAP have undergone reassessment. This discussion primarily will cover CMAPs recorded from normal muscle, with a brief discussion of CMAPs in neuromuscular disorders and the implementation of CMAPs in newer applications such as MUNE.

2. Terminology history

Attempting to establish the precise origin of a term or technique can be difficult. In the seminal paper describing the in vivo motor conductions in humans (Hodes et al., 1948), the evoked potential was termed the "Muscle Action Potential". Other early authors used the term "M wave". A review of early editions of textbooks on neuromuscular disease and electromyography (e.g., Aminoff, 1978; Downie, 1974; Goodgold and Eberstein, 1972; Norris, 1963) show that the preferred term was Muscle Action Potential, and in some cases, "M Potential" (Brown, 1984). For motor nerve conduction studies (MNCS), these authors focused mainly on "terminal latency" (now termed distal latency) and "conduction rate" (i.e., conduction velocity). In their seminal study, Hodes et al., 1948) provided amplitude reference values for the "muscle action potentials", but other early authors did not, since this was thought



Site	Latency (ms)	Amplitude (mV)	Velocity (m/s)
Wrist	3.0	6.9	(27)
Elbow	7.0	6.5	55

Fig. 1. Generation and measurement of the compound muscle action potential (CMAP). (A) Schematic of a motor unit (MU) and a surface recorded motor unit potential (SMUP). (B) Schematic supramaximal stimulation of a nerve with 4 axons. The shaded area indicates the variable progress of AP propagation from the cathode. Note the variation in the shape as well as latency of different SMUPs. (C) CMAP recorded from the abductor pollicis brevis muscle with median nerve stimulation. Markers 1 to 5 represent the onset, negative peak, baseline crossing, positive peak and the end, respectively. Marker 1 latency is the onset latency. The negative peak amplitude is voltage difference between marker locations 1 (usually on baseline) and 2 (at the peak). The negative peak duration is the time difference between markers 3 and 1.Total duration is between marker 5 and 1. The area, indicated in shading, is measured between the waveform and baseline. (with permission, S.D. Nandedkar, Ph.D.).

irrelevant when using needle recording electrodes (Aminoff, 1978; Downie, 1974; Goodgold and Eberstein, 1972). Over time, surface recording electrodes became the recording electrodes of choice.

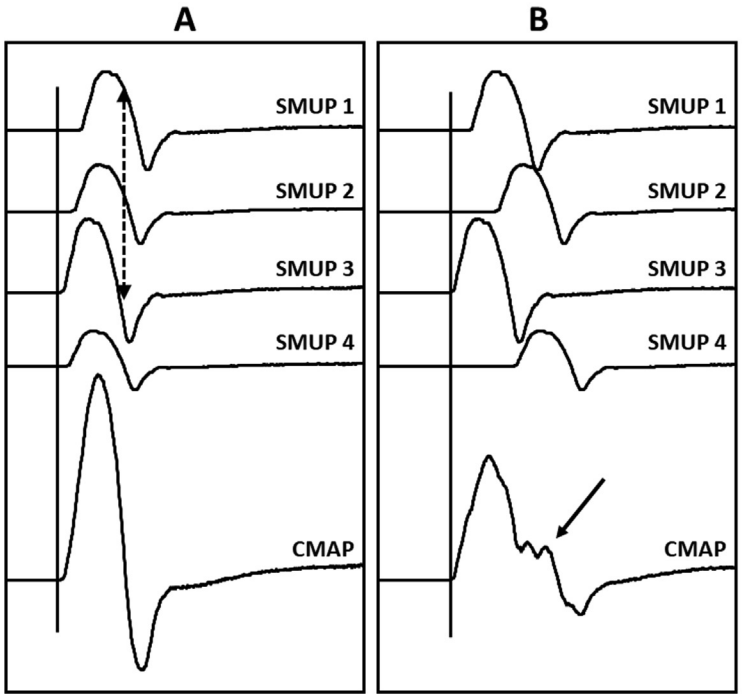
The origin of the term CMAP is unclear. It is not mentioned in Simpson's 1969 subcommittee report on terminology (Simpson, 1969). The first author of this review contacted available members of the 1980 Nomenclature Committee from the American Association of Electromyography and Electrodiagnosis (AAEE, currently the American Association of Neuromuscular and Electrodiagnostic Medicine [AANEM]). None could precisely date the origin or place for the term CMAP (Drs. C. Jablecki, M. Brandstater, and J. Albers, personal communications) but the term CMAP was included in their 1980 Glossary of Terms (AAEE, 1980). The 1983 international body's recommendations on terminology also included the term CMAP (International Federation of Societies for Electroencephalography and Clinical Neurophysiology, 1983). The earliest use of the term CMAP in a publication that we have found was by Daube and Lambert (1973). We suggest that the term CMAP probably arose by analogy with the concept of the compound nature of the nerve action potential that was introduced by Erlanger et al. (1924) in their work in St Louis MO, using the inertia-free cathode ray oscilloscope for their recordings; work that was recognized by the award of the Nobel prize to Gasser and Erlanger in 1944. CMAP, a term recognizing its multi-potential nature of the waveform, was thus a better explication than M-wave.

In motor nerve conduction studies, the motor response evoked by an electrical stimulus to its motor nerve is defined as the M wave (Dengler et al., 2020). In current practice, CMAP is the most commonly used term in MNCS (Stålberg et al., 2019). While the CMAP is "the summation of nearly synchronous muscle fiber action potentials recorded from a muscle" resulting from a stimulus (Dengler et al., 2020), this overlooks the critical underlying variable, the motor units (MU) themselves. Although the individual muscle fiber (MF) action potentials (APs) are the basic generators of the waveform, the SMUPs are the fundamental components of the CMAP (M wave). The word "action" in CMAP indicates that this potential arises as a result of nerve stimulation, not from spontaneous MF activity. Thus, the CMAP is not an AP per se, but is a compound potential derived from the MF APs comprising the MUs that in turn summate to form the CMAP (i.e., a derivative signal from the MF APs). Despite the codification of these terms (Dengler et al., 2020), there has been a change in usage such that the term CMAP has largely displaced the term M wave. Note that the definitions of CMAP and M−wave do not define the shape, amplitude or duration of the response, nor is there any description of whether or not the motor response is due to a supramaximal motor nerve stimulus. Though strictly speaking a misnomer, the term CMAP will be used in this review.

3. Generation of the CMAP

MFs are organized in functional entities termed motor units (MUs). A MU consists of a motor neuron (MN), its axon and all the MFs that it innervates through its motor endplates (Fig. 1A) (Sherrington, 1929). Although a muscle is innervated by only one nerve, a single nerve may innervate multiple muscles. When a nerve is stimulated, it will excite all the muscles it innervates distal to the stimulation site; it will also send an antidromic impulse (i.e., cephalad) that may generate an F wave.

The number of MFs innervated by a motor axon vary depending on the muscle (Feinstein et al., 1955) as well as their location in the muscle and whether they are type1 or type2 units. This number is termed the "innervation ratio". Recent work has shown considerable complexity in the spatial arrangement and shape of MUs in individual muscles (Heskamp et al., 2022).



C

SMUP	Amplitude (μV)	Area (μV x ms)	Duration (ms)
1	100	210	3.25
2	80	168	3.25
3	125	263	3.25
4	60	126	3.25
Total	365	767	

D

Measurement	CMAP (A)	CMAP (B)
Latency (ms)	3	4
Amplitude (μV)	339	210
Area (μV x ms)	729	594
Duration (ms)	3.65	6

Fig. 2. Temporal dispersion and compound muscle action potential (CMAP) measurements are illustrated schematically from a muscle innervated by 4 axons. The surface recorded motor unit potentials (SMUPs) from the 4 motor units are shown in the top in A and B. Their sum is the CMAP shown in the bottom trace. For simplification, the SMUP waveforms are identical (same duration) but have different amplitude and area. They are asynchronous due to temporal dispersion that is much higher in B than in A. The individual SMUP measurements are shown in top table in C. If there was no temporal dispersion, the CMAP amplitude and area would be the sum of all SMUP amplitude and area, respectively. Due to dispersion and resulting phase cancellation the CMAP amplitude and area are less than the sum (bottom table). (D) Comparing CMAPs in A and B, the area decreased far less compared to amplitude. The duration is higher in B. (with permission, S.D. Nandedkar, Ph.D.).

Any muscle can be used for recording a CMAP, e.g., following ulnar nerve stimulation, the abductor digiti minimi (ADM), first dorsal interosseous (FDI) or palmar interosseous muscles. The CMAP is recorded using three electrodes and a differential amplifier. The close placement of the recording electrodes allows one to attenuate (but not eliminate) potentials from other near and distant co-stimulated muscles (so-called "crosstalk"). As it is a composite signal, the CMAP recording from the medial hand is sometimes, for convenience, called the hypothenar CMAP, although the recording electrode is anatomically over the ADM muscle.

When stimulated, an axon produces an AP that propagates bidirectionally. Antidromic propagation may lead to a late response (e.g., an F wave), which we will not discuss further. The orthodromically propagated AP travels along the axon into its many terminal branches that supply the individual MFs of the MUs. Once the nerve AP excite the presynaptic terminals of the neuromuscular junctions (NMJs) of all the MFs that it innervates, the MFs generate their own postsynaptic muscle APs that propagate, more slowly than nerve APs, bidirectionally from their endplates to their tendinous ends. The summated electrical potential from all the MFs in a MU is its motor unit potential (MUP) (Fig. 1A) (Barkhaus and Nandedkar, 2008; Nandedkar and Barkhaus, 2013a).

Thus, in stimulating one axon, the APs from many MFs are almost simultaneously recorded. These APs are summated which leads to an increased amplitude response compared to the nerve AP. This is termed "biologic amplification" (or "the magnification effect") in the context of MNCS. In clinical practice, MUPs are typically investigated using needle electrodes (i.e., electromyography [EMG]). However, a surface electrode (SE) can also record the MU signal. This is termed the surface recorded MUP (SMUP) (Fig. 1A).

In a MNCS, the nerve is stimulated at an intensity level (supramaximal) that excites all the axons. As a result, all MUs in the muscle are believed to be activated. The CMAP is the summation of all SMUPs from the MUs within the recording territory of the surface electrode (Fig. 1B, Fig. 2A,B).

4. CMAP measurements and their anatomic correlates

4.1. Overview

On the display screen (Fig. 1C), the vertical (y) axis measures the signal's voltage (millivolts); this is used to measure the CMAP amplitude. In nerve conduction studies, a negative voltage, by international convention, is set to be displayed on screen as an upward deflection, and vice versa. The horizontal (x) axis on the screen measures the timing of the signal (msec). This includes the onset latency, negative peak latency, and the point where the negative going peak of the CMAP intersects the baseline (Fig. 1C, markers 1, 2 and 3, respectively). These points allow measurement of CMAP latency, negative peak amplitude, negative peak area, and negative peak duration. The latter is defined as the first negative-to-positive baseline crossing after the first negative peak (Barkhaus and Nandedkar, 2008; Stålberg, et al., 2019).

Additional markers can be placed for the positive peak (Fig. 1C, marker 4) and the point where the positive phase returns to baseline (marker 5). They are used in measuring peak-to-peak CMAP amplitude, total area, total duration, etc. Total duration is measured from signal onset to its return to baseline after the last positive peak. As the positive phase may be affected by the electrode position(e.g., E2 [see section 6.10], and other variables), these parameters are not commonly used. However total CMAP duration may be useful in the setting of very complex CMAPs as in acquired demyelinating conditions. In this discussion, the amplitude, area,

and duration will refer to measurements from the negative peak, unless otherwise indicated.

Measurement of conduction velocity is the oldest measured parameter (Helmholtz, 1850). It is calculated after stimulating the nerve at two sites (Fig. 1C). The site closest to the recording electrode is called 'distal' and the other site is proximal (based on their distance from the motor neuron in the spinal cord).

$$\text{Velocity} = \text{Distance between stimulation sites}/(\text{Proximal latency} - \text{Distal latency})$$

In the above formula, the distance is in millimeters and the latency difference in milliseconds. One can also stimulate the nerve at multiple sites and use different combinations of stimulation sites to assess velocity in different segments of a nerve. Amplitude, duration, and area can be measured and compared at the different stimulation sites.

4.2. Latency and velocity

When a nerve is stimulated, all its axons under the cathode are simultaneously depolarized. AP propagation velocity varies between axons based on their diameter (large diameter fibers conduct faster than small ones). Although the motor nerve fibers have similar diameters, there is some variation. Hence, there is some variation in time for the nerve APs to reach the MFs (Fig. 1B). Because of variation in MF diameters within the same MU, there is also some variation in the propagation of the MF APs forming the SMUP. In addition, the motor endplates are scattered, unrelated to axon velocity, within a regular (biceps) or complex (soleus) endplate zone (Aquilonius et al., 1984; Askmark et al., 1985; Stålberg and Dioszeghy, 1991; van Dijk et al., 1999). Thus, the individual SMUPs are not synchronous (Fig. 1B, 2). This phenomenon is called "temporal dispersion" which is a normal physiological phenomenon, but which may be increased in neuromuscular disorders (Fig. 2B).

Since the CMAP is the sum of its constituent SMUPs, its composition is determined by the generation of the SMUPs reflecting AP propagation by the motor axons (Fig. 2A, B). In pathology, the conduction velocity may decrease, but it never increases. Very short latencies in recordings using standard conduction distances should be assessed with caution, as they are likely technical or anatomic artifacts.

Onset latency represents the time between nerve stimulation to the beginning of the CMAP (Fig. 1C, D). It is contingent on the distance between the stimulating and recording sites. To quantify the distal latency, the distal stimulation site is measured at a fixed distance proximal to the recording electrode (e.g., 7 cm at the wrist). This approach may be impractical in very young children and infants; anatomical landmarks may then be preferred.

The latency includes the time of nerve AP propagation along the myelinated portion of the motor axons in addition to other events. Motor nerve AP propagation is slower in the smaller diameter terminal axon branches (Fig. 1A). The latency also includes time required for neuromuscular transmission (about 1 ms), time for generating the muscle APs, etc. These events are common to both stimulation sites and are cancelled by the CV formula (section 4.1). The calculation reflects the velocity from the nerve segment between the stimulation sites. Calculating velocity as the ratio of distance to latency from a single stimulation site will give a falsely low velocity value indicated in parentheses (Fig. 1D) and is not recommended. Other strategies have been proposed to better assess the latency and conduction at the distal site (Lupu et al., 2007; Uzar et al., 2011):

$$\text{Residual latency} = \text{Distal latency} - (\text{Distance}/\text{Proximal Conduction velocity})$$

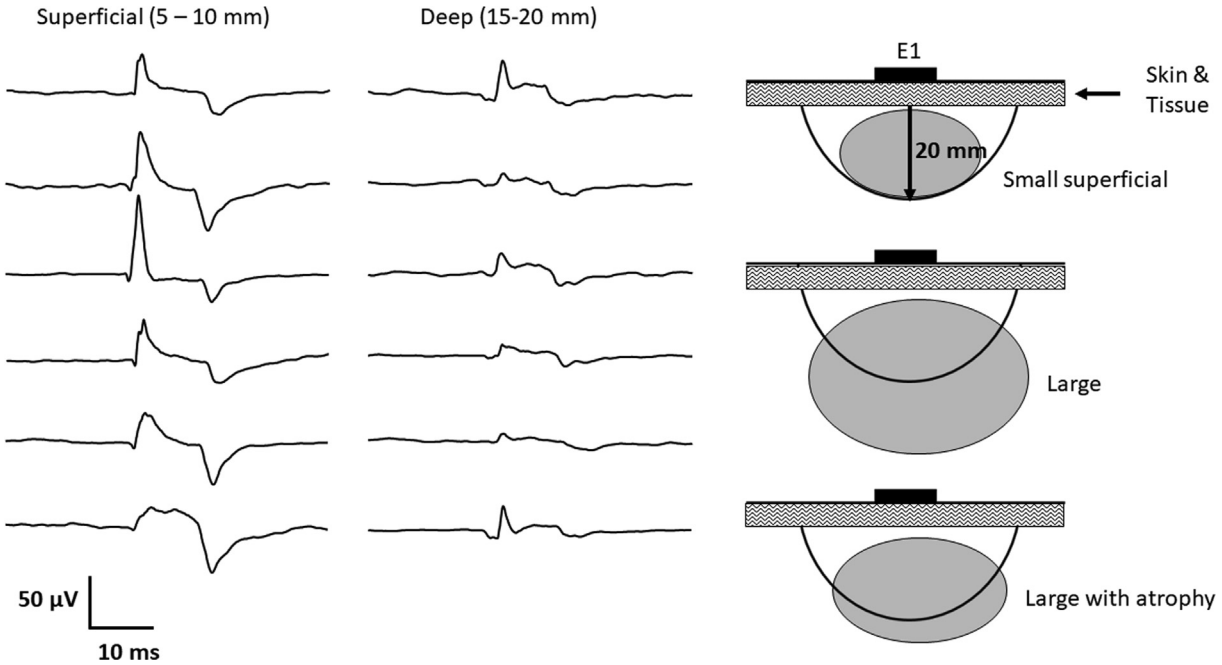


Fig. 3. Surface recorded motor unit potentials (SMUP) from the biceps muscle of a healthy subject. An intramuscular needle was used to identify discharges from a single motor unit and estimate its depth from the skin surface. The time-locked activity from surface recordings was averaged. The E1 was over the mid-belly of the muscle over the endplates. Hence the SMUP has an initial negative deflection. Note the broad SMUP with duration of 15–20 ms. The force of contraction was low and similar in all recordings. The amplitude of SMUP from deeper MUs is lower. This demonstrates the limited recording territory of the surface electrode shown as a semi-circle on the right. The overlap of muscle cross section with the uptake area for a small, large, and large muscle with atrophy is shown. See text for details. (with permission, S.D. Nandedkar, Ph.D.).

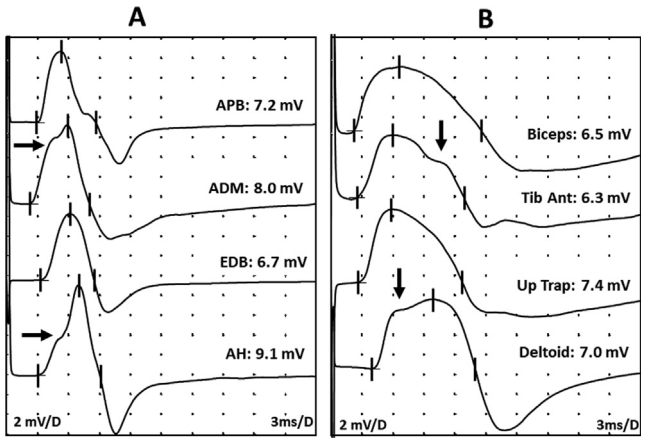


Fig. 4. The compound muscle action potential (CMAP) was recorded from commonly tested (A) small and (B) large limb muscles of a healthy subject. Note the similar amplitude for all muscles despite significant different in the size and strength of these muscles. Note the longer duration and hence higher area for the large muscles. Dark arrows indicate a "shoulder" in the CMAP, usually due to the E2 electrode. (with permission, S.D. Nandedkar, Ph.D.).

$$\text{Terminal latency index} = (\text{Distance}/\text{Proximal Conduction velocity})/\text{Latency}$$

In the above formulae, the distance is measured between the stimulating and recording sites.

4.3. Amplitude, Area, and duration

Due to differences in MUs and technical factors SMUPs are not identical (see section 6). MU size refers to the number and size of the MFs comprising the MU. Larger MUs have a greater SMUP amplitude, however this effect is mitigated by the distance of the MU from the surface electrode. CMAP size reflects the number and size of its constituent MUs. It can be reduced due to loss of MUs (e.g., a neurogenic process), due to reduced MU size (e.g., MF loss as in a myopathic process), or an endplate disorder (either pre-synaptic or severe post-synaptic transmission dysfunction).

Desynchronization of SMUPs, i.e., temporal dispersion, leads to a phenomenon called "phase cancellation". Its effects on the CMAP are illustrated schematically in Fig. 2. In A, the negative phase of SMUP 1 occurs when the SMUP 3 has a positive phase (Fig. 2A, dashed arrow). Hence, the contribution of SMUP 1 to the CMAP is reduced. Note that the CMAP amplitude (339 μV) is less than the sum of individual SMUPs (365 μV). AS temporal dispersion in motor nerve APs increases, CMAP amplitude decreases due to phase cancellation (Fig. 2B,D).

Temporal dispersion is also reflected in CMAP duration (Olney et al., 1987). If all SMUPs are synchronous, CMAP and SMUP durations will be the same. When abnormal temporal dispersion is present, CMAP duration will be affected more than SMUP duration. This is because the increased temporal dispersion is mainly reflected by the variation in motor axon conduction velocities of the different MUs.

Temporal dispersion increases CMAP duration while concomitantly decreasing CMAP amplitude. Imagine the CMAP's negative phase as a triangle. Widening the base while reducing the amplitude will relatively preserve the area of the triangle. This analogy also applies to changes in CMAP. In Fig. 2, increasing temporal dispersion increased the duration by 64 % while the amplitude was reduced by 38 %: CMAP area was decreased by only 18 %. Therefore, this observation did not fulfill the criteria for partial conduction block (AANEM, 1999; Brown and Feasby, 1984). Increased temporal dispersion often makes the waveform appear serrated with multiple peaks and/or phases. In such waveforms one should measure the negative peak duration using the last negative to positive baseline crossing as the reference point.

5. Recording electrode and its uptake area

The theoretical concept of a MUP is quite simple: it is the summated electrical activity from all the MFs in the MU. However, this is not what we measure. Recall Heisenberg's quote, "Since the measuring device has been constructed by the observer... We have to remember that what we observe is not nature itself, but nature exposed to our method of questioning" (Heisenberg, 1958). Thus, our observations of the MUP are dependent on how we record it (i.e., the recording device itself). The SMUP contributing to the

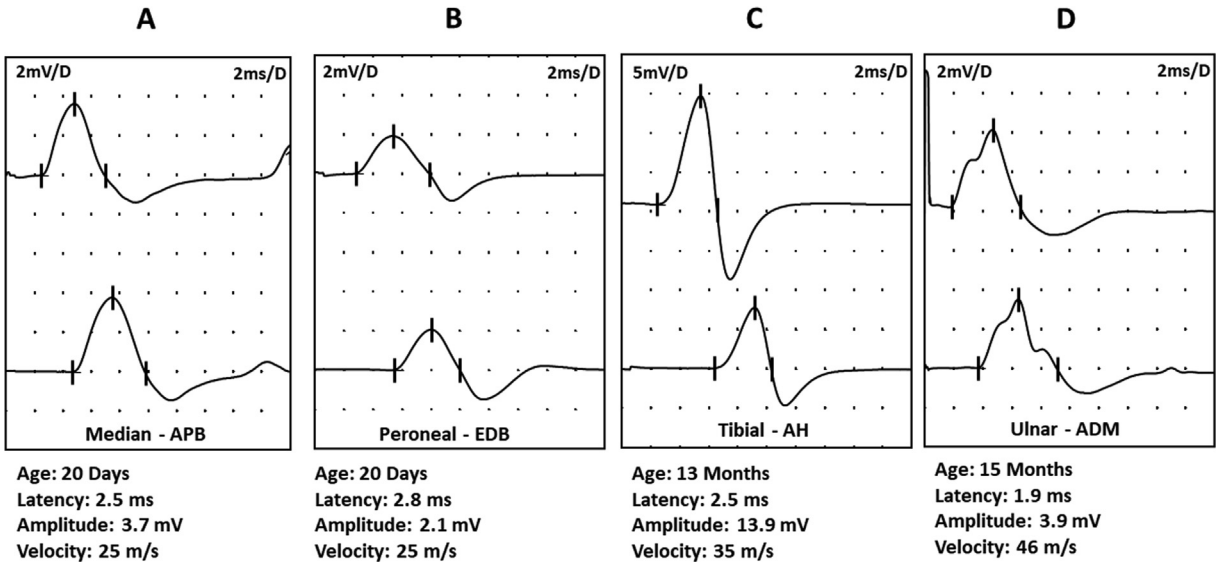


Fig. 5. The compound muscle action potential (CMAP) recorded from commonly tested muscle in pediatric patients. (A, B) 20 days old (C) 13 months old and (D) 15 months old. (with permission, P.E. Barkhaus, M.D.).

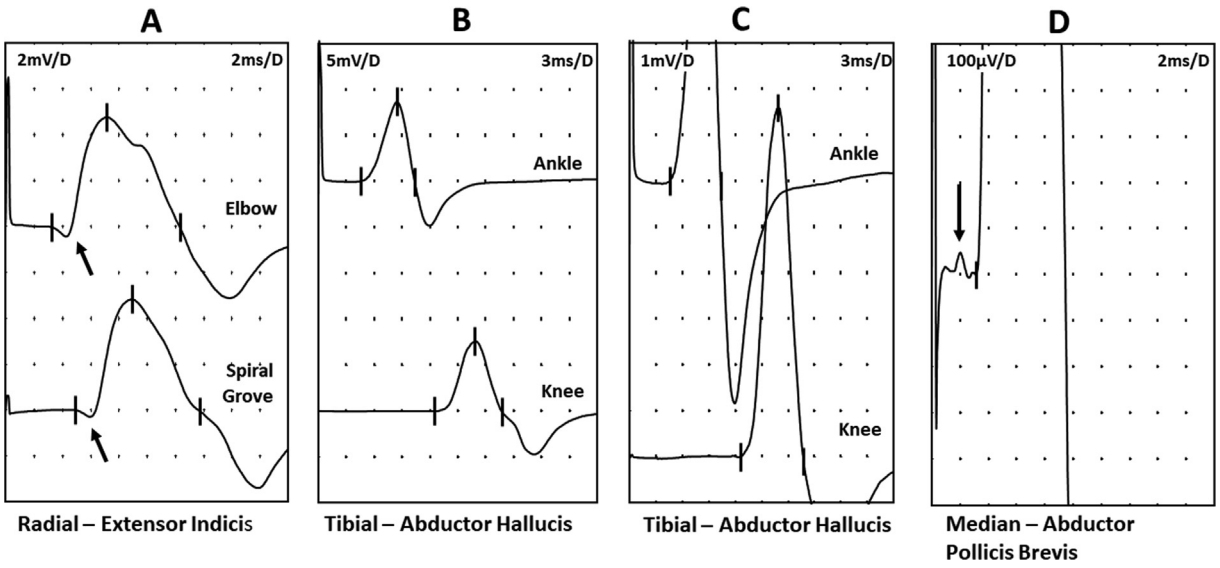


Fig. 6. Technical aspects (A) CMAP recording from the Extensor indicis muscle shows an initial positive deflection at both stimulation sites despite changing the E1 position. Onset can be defined as the first deflection from baseline or the beginning of the negative peak. (B, C) CMAP recorded from the abductor hallucis brevis muscle with ankle and knee stimulation. In B, the latency maker may appear incorrect. At higher display sensitivity in C, the position appears correct. (D) Pre-motor potential in a median nerve conduction study. (with permission, S.D. Nandedkar, Ph.D.).

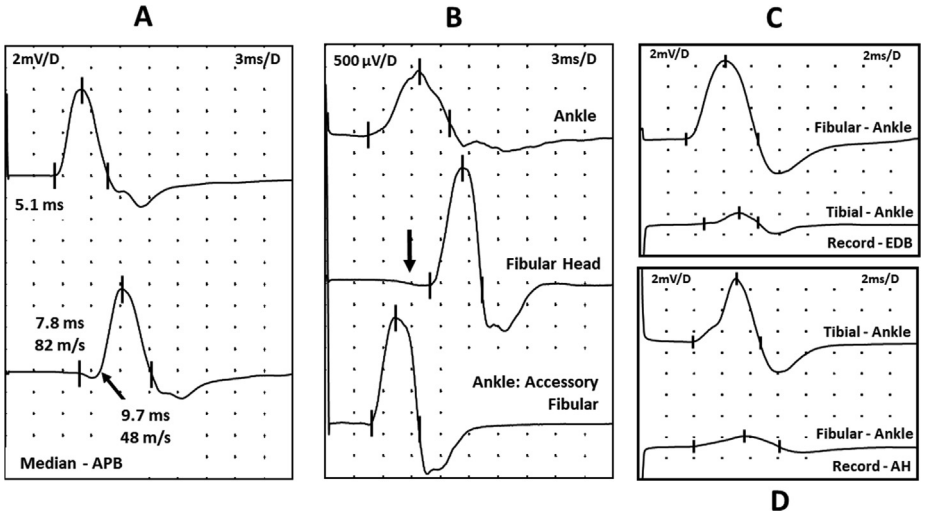


Fig. 7. CMAP waveform and anastomosis (A) Martin-Gruber anastomosis in a patient with carpal tunnel syndrome. Arrow indicates recommended position for latency and amplitude measurement. (B) Accessory fibular nerve innervation to extensor digitorum brevis EDB). (C) Top trace: The expected EDB CMAP recorded from a normal individual with distal fibular nerve stimulation. The lower trace shows "apparent" innervation of extensor digitorum brevis (EDB) using the same montage but with the distal tibial nerve stimulation. The signal shown is a far-field potential and not a response from EDB (see section 7.2 for details). (D) Top trace: The expected abductor hallucis CMAP recorded from a normal individual with distal tibial nerve stimulation. The lower trace shows "apparent" innervation of abductor hallucis using the same montage but with the distal fibular nerve stimulation. Again, as in (C), the signal shown is a far-field potential and not a response from the EDB (see section 7.2 for details). (with permission, S.D. Nandedkar, Ph.D.).

CMAP (Fig. 3) is quite different from the sharp-rising, multi-phasic waveform seen on needle EMG.

Fig. 3 shows SMUP recordings from the biceps muscle of a normal subject using the technique of spike-triggered averaging (Nandedkar and Barkhaus, 1987). The surface electrode is superficial and at variable distance from the generators of the signals (i.e., MFs). The high frequency components of the MUP are attenuated by the tissue underlying the surface electrode. Hence the SMUP is mainly a low frequency signal and does not exhibit sharp components. When the recording electrode is over the endplate zone, it has a biphasic waveform (Dumitru et al., 2023). All electrical fields decline in amplitude as the distance between the generator and recording electrode is increased. A surface electrode mainly records activity from generators that are within 20 mm from the skin surface (Fig. 3) (Barkhaus and Nandedkar, 1994). Thus, tissue edema or increased skin thickness will impact CMAP amplitude as the distance from the surface electrode to the generators (MFs) will be increased.

This recording territory may include the entire cross section of a small superficial muscle (e.g., abductor pollicis brevis [APB]), but is insufficient to record from all the MFs and MUs of large muscles (e.g., biceps brachii). Thus, the CMAP of a large muscle will not comprise the electrical activity of the entire muscle. The similar amount of muscle in cross section within the surface electrode's

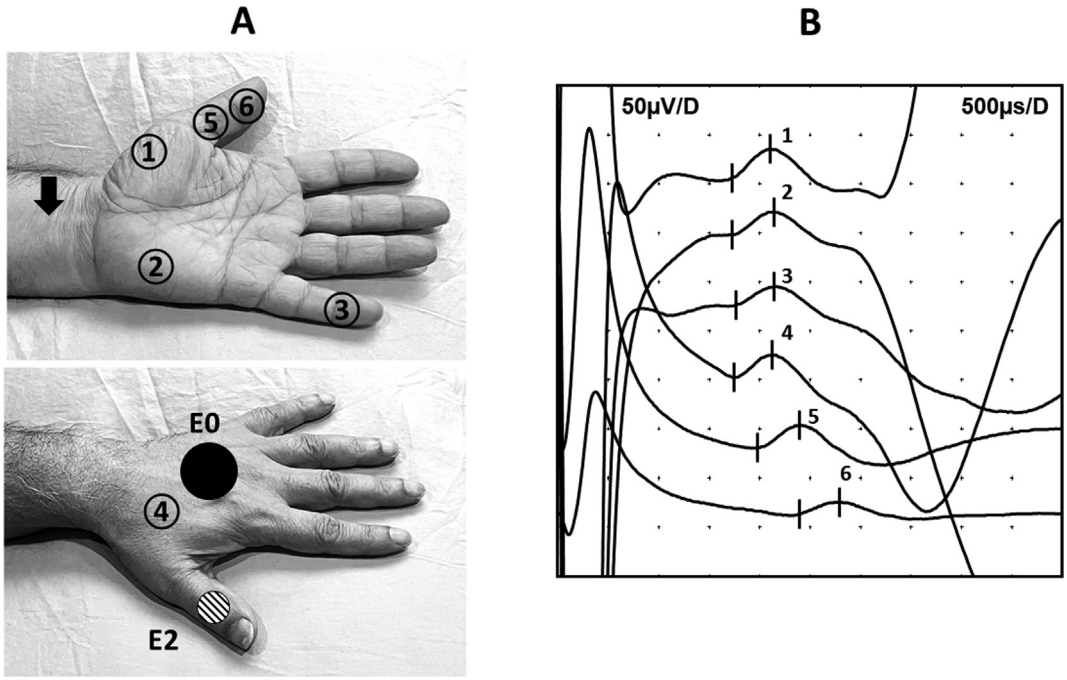
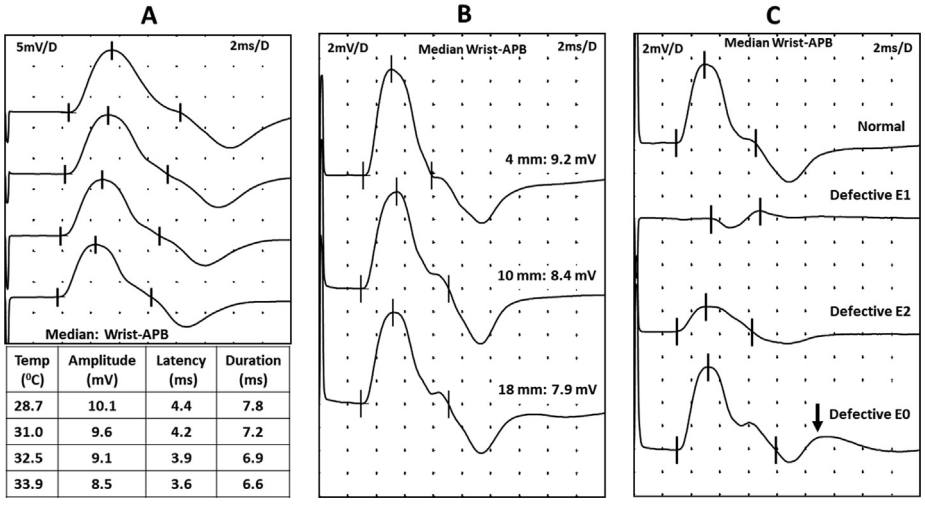


Fig. 8. The origin of pre-motor potential is investigated. (A) Position of E1 electrode. Arrow indicates the stimulation site (B) The response in the top 4 traces is the pre-motor potential. The bottom two traces are from propagating nerve action potentials. See text (6.1) for details.



Temp (°C)	Amplitude (mV)	Latency (ms)	Duration (ms)
28.7	10.1	4.4	7.8
31.0	9.6	4.2	7.2
32.5	9.1	3.9	6.9
33.9	8.5	3.6	6.6

Fig. 9. Technical aspects. (A) Effect of temperature. The limb was cold when the first response was recorded. Note the change in CMAP when the limb was warmed. (B) Smaller recording surface gives higher amplitude (C) Defective leads. See text (6.2, 6.4, 6.5) for details. (with permission, S.D. Nandedkar, Ph.D.).

uptake area for both small and large muscles will result in similar CMAP amplitudes (Fig. 3). This is readily seen in CMAP recordings from large and small muscles of a healthy subject (Fig. 4) (Barkhaus and Nandedkar, 1994). Because of this limitation in the uptake area, the CMAP amplitude in pediatric studies is also relatively high and comparable to the CMAP amplitude in adults despite the obvious difference in muscle size. Fig. 5 shows CMAP recordings from different pediatric subjects. The 13-month-old subject has a very robust amplitude (13.9 mV) from the abductor hallucis (AH). The 20-day old subject has an APB CMAP amplitude of 3.7 mV compared to a lower limit of 4.4 mV for adult subjects in our laboratory. The extensor digitorum brevis and ADM amplitudes also show the same pattern.

In large muscles, whether of pennate or strap morphology, the MFs are longer. It therefore requires more time for the muscle AP to travel from the endplate zone to the tendons. Hence, such muscles have longer duration SMUPs. Note that SMUPs in the biceps brachii (Fig. 3) have durations of 15–20 ms compared to the APB (less than 10 ms). Long duration SMUPs result in longer CMAP duration with concomitant larger CMAP area (Barkhaus and Nandedkar, 1994; Kimura et al., 1986; Lateva et al., 1996; van Dijk et al., 1994).

6. Technical considerations in recording the CMAP

6.1. Display and measurements

When CMAPs are biphasic with initial negative deflection (Fig. 1C), the onset latencies of the distal and proximal CMAPs

are easily identified. Measurements are simple as it is inferred that the surface electrode overlies the endplate zone (Dumitru et al., 2023). CMAP amplitude is measured from baseline (where onset marker is placed) to negative peak. When an initial positive wave occurs at a stimulation site that cannot be eliminated by adjusting the recording electrode position, latency should be measured from the initial positive deflection. Conduction velocity can be derived from the points at which the initial positive deflections occur or at the onset of the negative going response (Fig. 6A). Whichever is used, the same paired point of measurement must be used for calculation (Stålberg et al., 2019). When initial positive deflection occurs on proximal stimulation, amplitude, latency, and velocity should be measured using the baseline crossing at the end of the initial positive peak (Fig. 7A). Note that measurements should be performed to corresponding points of the signal for distal and proximal stimulation.

To ensure clarity and good quality signals and measurements, all CMAP recordings should be displayed at a sensitivity such that the peak deflection exceeds at least one vertical division of the grid on the screen (Fig. 6A, B). To avoid error that may occur in CMAPs with slow rise times (onset latency to time of maximum negative peak amplitude), onset latency measurements should be made at a standard high sensitivity setting such as 200 or 500 μV/division (Falck and Stålberg, 1995). This is often seen in the lower limb, especially in tibial motor conduction studies in which rise time at the proximal stimulation site may appear slow in normal (especially tall) individuals (Fig. 6B, C).

Median nerve CMAPs at high sensitivity settings may show a very small negative potential preceding the main waveform (Fig. 6D). This is termed the "premotor potential" (PMP) and is considered to be a far-field potential (Dumitru and King, 1995) As the PMP has been previously considered a sensory afferent response, the following experiment corroborates the work of Dumitru and King (1995).

The median nerve was stimulated at the wrist using supramaximal intensity (Fig. 8). The response was recorded from 6 different positions of the E1 electrode. The E2 and E0 positions remained the same in all recordings. All traces show a low amplitude potential, but its interpretation is quite different. In traces 1–4 the potential has the same latency and similar waveform despite different E1 positions. Hence this is a far field recording and is the PMP. The large amplitude signal following the PMP is the motor response. It varies considerably with E1 position.

When E1 is over the thumb (positions 5 and 6), the latency increases with the distance from stimulation site. This is the near field sensory nerve action potential recording and demonstrates propagation of the AP. The PMP latency in traces 1–4 corresponds to arrival of propagating nerve AP at the metacarpophalangeal junction of thumb. The PMP is generated by the dipole moment imbalance when the sensory nerve action potentials cross this junction. It is seen readily seen when the recording electrodes are on the opposite sides of the junction (positions 1 – 4). At positions 5 and 6, the E1 and E2 electrodes are close to each other. They record a similar motor response that is cancelled by the differential amplifier. Hence, only the propagating sensory nerve AP is seen. As a far field potential, it should not be used in measurement of the CMAP.

6.2. Temperature

Cooling has a marked effect on nerve conductions and is a common cause of technical error. In this review, its influence will be confined to the CMAP. Reduced temperature requires more current for depolarization and leads to increased times for depolarization and repolarization, due to prolonged opening times of the Na + and K + channels. This results in both a slowed CMAP rise time and return to baseline with consequent increases in CMAP latency, amplitude, area, and negative duration (Fig. 9A) (Dioszeghy and Stålberg, 1992; Franssen et al., 1999; Rutkove, 2001).

There are corrective factors and equations to adjust for reduced limb temperature. However, these should be used with caution as they assume that the skin surface temperature represents the actual temperature of the underlying nerve and muscle. They also assume that corrective factors apply similarly to both normal and abnormal nerve and muscle. There are numerous methods of warming and maintaining warmth in limbs that should always be applied as necessary. External radiant heat may not warm deep tissues for some considerable time. Immersion of the limb in warm water is the best way to achieve thorough, homogeneous deep tissue warming (Rutkove, 2001).

6.3. Recording electrode Nomenclature

CMAPs are recorded with surface electrodes in most instances (see below). Terminology for these vary, with G1 and G2 used in older literature but now discouraged (Dengler et al., 2020). The terms "active" (for G1), "reference" (G2), and "ground" electrodes are commonly used. However, the "reference" electrode is also an "active" electrode, and the "ground" electrode is not a true ground electrode. (Robinson et al., 2016; Robinson et al., 2017). This review will use the terms "E1", "E2", and "E0" electrodes in lieu of active, reference, and ground electrodes, respectively (Dumitru and King, 1995; Stålberg et al., 2019).

6.4. Selectivity, size and geometry of recording electrodes

The single MF AP is studied theoretically using a point electrode (Nandedkar and Stålberg, 1983(a); Plonsey, 1974). Since the electrodes used in clinical studies have a finite surface area, the potential is obtained by averaging the signal over the electrode's recording surface (Nandedkar and Stålberg, 1983(b)). Some areas of the recording electrode are away from the MFs and will record smaller signal. This effect is more prominent when the electrode is large. Thus, the net effect is a smaller CMAP amplitude signal when the recording surface is large. For the same reason, the CMAP will be larger when recorded with a smaller surface electrode (Fig. 9B). SMUP amplitudes recorded by standard surface electrodes that are circular with 10 – 18 mm diameter range from around 20 μV to < 200 μV in normal subjects (Barkhaus and Nandedkar, 1994). In contrast, MUPs recorded with concentric needle electrodes of surface area 0.07 mm^2, or monopolar needle electrodes, in normal subjects range from 200 μV to just over 5000 μV, depending on the muscle and age.

While larger recording electrode areas give lower amplitude CMAPs, they also make recordings more reproducible (Barkhaus et al., 2006; Jonas et al., 1999; Tjon-A-Tsien et al., 1996; van Dijk et al., 1995). Excessively large electrodes will give much lower amplitude CMAP. Furthermore, they risk contamination by signals from other overlapped muscles. Hence the CMAP is typically recorded by a surface electrode of 10–18 mm diameter or length.

Some authors advocate for larger surface electrode size to promote reproducibility in performing motor conduction studies (van Dijk et al., 1995) and for use in recordings from large proximal muscles. (Tjon-A-Tsien et al., 1996) There is no simple solution to this dilemma, as it is impractical to use different size electrodes in everyday work. One must decide between the benefit of higher amplitude using smaller surface electrodes versus better reproducibility using larger recording electrodes. This is a particular issue in very young children and infants where standard size surface electrodes may easily exceed the size of the muscle. In the latter instance, the smallest commercial electrode size may be necessary for an optimal CMAP recording; these may even require

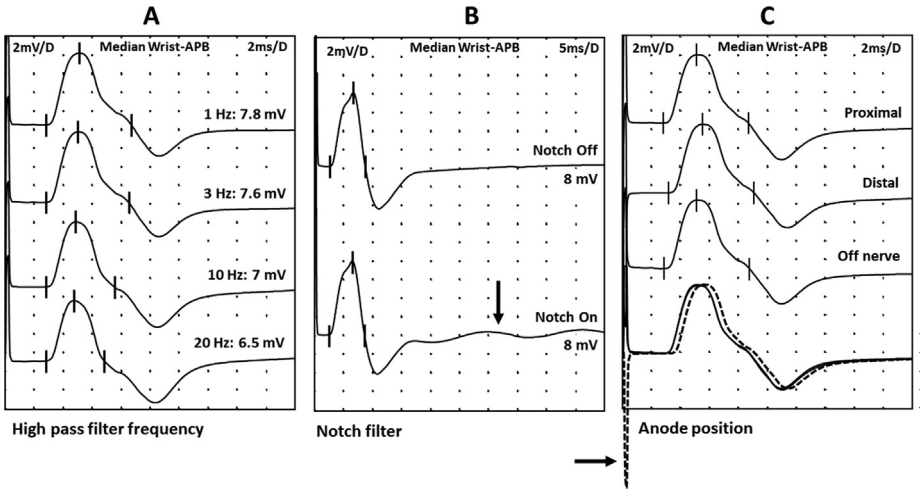


Fig. 10. Technical aspects. (A) Increasing high pass frequency (B) Effect of notch filter (C) Anode position relative to cathode and nerve. See text for details (6.6, 6.7). (with permission, S.D. Nandedkar, Ph.D.).

further cutting down in size with scissors, for example, in neonates and infants.

Surface electrode shape also influences CMAP amplitude. Circular electrodes record a larger amplitude CMAP signal than rectangular electrodes of equal area (Barkhaus et al., 2006). In a circular electrode there is less variability in distances between the generators (i.e., the MFs constituting the SMUPS) and the electrode (since the electrode "senses" the MF generators differently at different points on the electrode's recording surface). By virtue of its geometry, a rectangular electrode will have greater variation in these distances (Barkhaus et al., 2006). If a rectangular electrode is used, the longer side should be perpendicular to the direction of the MFs that are being recorded. Both self-adhesive circular and strip electrodes are commercially available.

Until recently, most laboratories made their recordings with reusable 10 mm diameter circular metal discs for E1 and E2. In pediatric studies, some investigators used 4 mm circular EEG surface electrodes for recordings. Disposable electrodes have gained popularity due to reduced risk for contamination and are used as standard practice in many laboratories. These electrodes are very convenient to use and eliminate the need to repeatedly apply gel as well as using sticky tape to secure them. These commercial surface electrodes already have adhesive and conductive gel and can be repositioned several times in studying multiple nerves. These are available in different sizes and shapes (circular and rectangular) and are slightly greater than 10 mm in length or diameter. As shown in Fig. 9B, larger, 18 mm diameter electrodes record slightly lower CMAP amplitude compared to 10 mm disc electrodes. However, this difference is small and is masked by variability in the CMAP due to the E1 position (section 6.8).

Earlier authors (Geddes, 1972; Licht, 1961) have discussed electrical skin resistance and surface electrodes, but there are no formal studies on these topics of which we are aware. Cleaning the skin or gentle rubbing with a very fine abrasive reduces skin resistance and thus improves signal quality (Nandedkar, 2016). This observation was made by Eichler who performed the first nerve conductions in humans (Pleuhs et al., 2024). Furthermore, it will also help to sustain their adhesive properties for multiple electrode placements. If the skin surface has surface contaminants (especially sweat and lotions), it will render the electrode less adhesive after just a few placements.

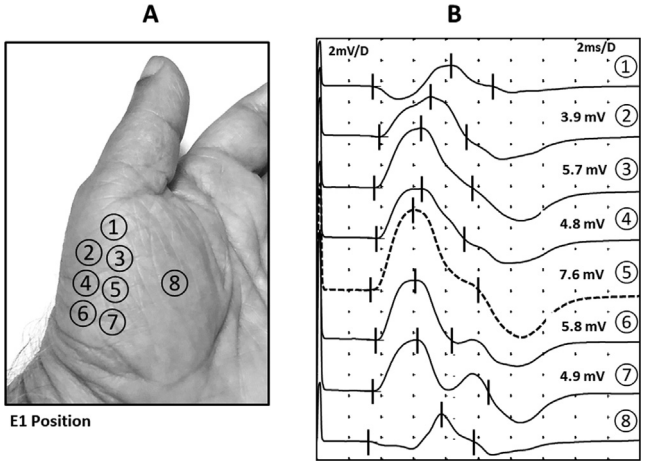
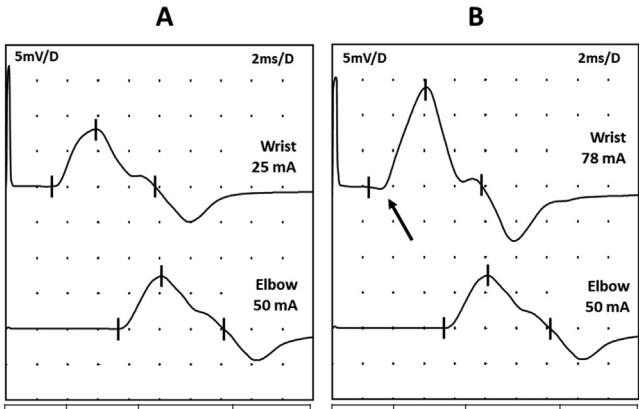


Fig. 11. Technical aspects. (A) Different E1 positions were used for recording the compound muscle action potential. The size of the recording surface is larger than indicated by the circles. Neighboring positions were separated by just a few millimeters. (B) CMAP recordings from different positions show significant change on amplitude and shape. Latency is less affected. See text (6.8) for details. See text (6.8) for details. (with permission, S.D. Nandedkar, Ph.D.).

6.5. Leads

It is necessary that all electrode leads make proper contact with the amplifier input circuitry and be of similar length. Defective leads confer different patterns to the CMAP (Fig. 9C) (Nandedkar and Barkhaus, 2023). The top trace shows the normal CMAP waveform. If the E1 lead is defective, a low amplitude CMAP is expected. When the E2 lead is defective, the CMAP has a normal appearance but low amplitude (third trace). Therefore, one should check both E1 and E2 electrodes and their leads when a low amplitude CMAP is encountered, particularly when it is inconsistent with muscle bulk. If the E0 lead is defective, the baseline may show a power line alternating frequency interference. The CMAP waveform, especially the terminal portion, will vary from one stimulus to next due to this interference (arrow on bottom trace). Interference may also be seen when E1 or E2 leads are defective (Fig. 9C).



Site	Latency (ms)	Amplitude (mV)	Velocity (m/s)
Wrist	3.0	8.1	---
Elbow	7.3	7.5	50

Site	Latency (ms)	Amplitude (mV)	Velocity (m/s)
Wrist	2.4	13.7	---
Elbow	7.3	7.5	43

Fig. 12. Technical aspects. (A) Median motor nerve conduction study with proper stimulus levels used for CMAP recordings. (B) With excessive stimulation at wrist, the ulnar nerve was co-stimulated. The CMAP waveform and measurements are affected. See text (6.8) for details. (with permission, S.D. Nandedkar, Ph.D.).

6.6. Filters

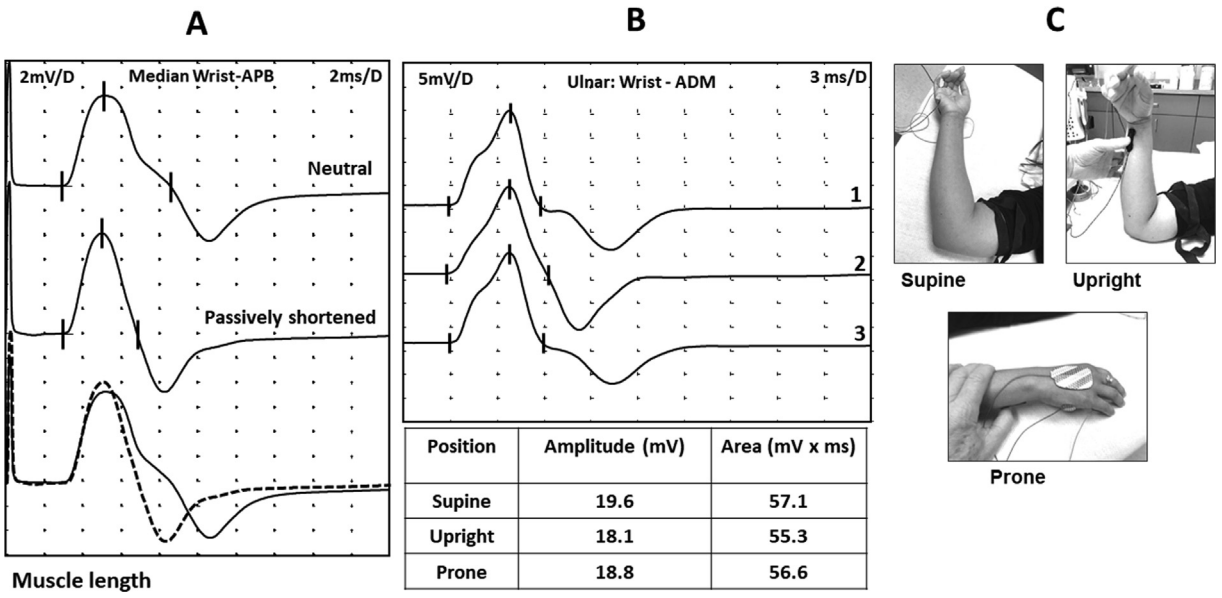
The CMAP contains a wide range of frequencies. To adequately record the CMAP onset without distortion from the stimulus artifact, the frequency bandwidth is typically 3 Hz-10KHz. Signals with frequency outside this range will be attenuated by the filters (Nandedkar and Mulot, 2019). Increasing the low frequency (high pass) filter will eliminate the low frequency components of the signal, causing the CMAP to have a lower amplitude, and shorter negative duration (Fig. 10A). Reducing the high frequency (low pass) filter will reduce high frequency amplifier noise but may result in reduced signal amplitude. As there are only minimal high frequency biological signals in the CMAP, the low pass filter would need to be significantly reduced (e.g., 1 kHz) to have an effect on the CMAP shape.

Most systems contain a "notch" filter that selectively excises the 50 or 60 Hz frequency that corresponds to the alternating current supply to the recording system. This can be a valuable tool for needle EMG and sensory nerve conduction studies when confronted with interference from other electrical devices such as in the intensive care unit. We recommend not using this notch filter for CMAP recording or in studies of late responses since it can affect the signal depending upon its implementation software. First, the CMAP amplitude may be reduced due to additional suppression of neighboring frequencies. Secondly, the notch filter may itself generate an artifact at power line frequency (Fig. 10B) (Nandedkar and Mulot, 2019; Nandedkar, 2019).

6.7. Stimulator orientation and placement

The electrical stimulator has two pin electrodes of differing polarity, the "cathode" (negative) and the "anode" (positive). In MNCS, the cathode is placed over the stimulation site. The anode is placed proximally over or near the nerve. During stimulation, the nerve APs develop under the cathode and pass orthodromically towards the muscle and antidromically towards the spinal cord. The primary role of the anode is to provide a return path for the stimulus current. The positivity created under the anode hyperpolarizes the nerve and may block the propagation of the AP. This is called "anodal block". In routine clinical recordings, anodal block is not seen. Fig. 10C shows CMAP recordings with the anode placed proximally (top trace) and distally (second) trace. In both positions the CMAP amplitude is unaffected indicating no block when the anode was placed distal to the cathode under standard recording conditions (2021b; 2021c; Nandedkar et al., 2021a; Nilsson et al., 1988).

CMAP latency is different however, when cathode and anode positions are reversed, because there will be differences in the distance between the cathode and E1. This is seen in the superimposed traces in Fig. 10C. In F wave recordings, however, one need not reverse the stimulator orientation because depolarization still occurs at the cathode. Not having to reverse the stimulator's position saves testing time. Some laboratories compromise and keep the cathode in place over the nerve but move the anode off the nerve (3rd trace) to ensure against an assumed anodal block.



Position	Amplitude (mV)	Area (mV x ms)
Supine	19.6	57.1
Upright	18.1	55.3
Prone	18.8	56.6

Fig. 13. Technical aspect. (A) Passive shortening of the APB muscle gives higher amplitude and shorter duration CMAP (B) Hand and finger position affects the CMAP from the hypothenar muscle group. See text (6.9) for details. (with permission, P.E. Barkhaus, M.D.).

6.8. Distal stimulation site and E1 placement

Assessment of the distal CMAP is based on a defined conduction distance. Begin by stimulating the distal nerve with a weak stimulus current. The intensity is then increased until a maximum CMAP amplitude is obtained. A further increase by 15–20 % is usually made to ensure supramaximal stimulation. The position of E1 is then adjusted as to reach a maximal CMAP amplitude (usually 3–4 times and usually by only a very small distance, 2–5 mm). Each new placement is followed by stimulation in order to record the largest amplitude CMAP (Fig. 11). This important guideline was clearly stated in the original paper by Hodes et al. (Hodes et al., 1948) but in practice it is often overlooked. It is a critical step in ensuring CMAP reproducibility (Nandedkar et al., 2010; Nandedkar et al., 2018).

Once E1′s position is ascertained, the distal conduction distance is measured and the final CMAP obtained at supramaximal stimulation and optimal E1 placement. If this is more proximal and the nerve's anatomic course is deeper and therefore more distant from the stimulator, the stimulus may need to be adjusted (increased). If the conduction distance places the distal stimulation site proximal to the site where the maximum CMAP amplitude was obtained, the CMAP's amplitude may appear decreased. The usual reason is that the nerve may be anatomically deeper (i.e., further) from the cathode. The stimulus intensity may therefore need to be further increased to ensure all motor nerve fibers are excited.

The tibial nerve is an exception, as the tibial CMAP recorded from the abductor hallucis (AH) is mostly derived from E2, a composite of the volume conducted CMAP recordings from the other foot muscles. Hence, the tibial CMAP is comprised of signals from multiple muscles, each comprising multiple SMUPs. When the stimulator placement is adjusted, so also is the temporal relationship of the tibial nerve's component CMAPs from these muscles, resulting in different appearance of the tibial CMAP due to phase cancellation (Barkhaus et al., 2011, Nandedkar et al., 2007).

If an adequate (but not excessive) stimulus is applied, depolarization will occur under the cathode. If the stimulus is further increased, the nerve may be stimulated distal to the cathode, shortening the latency, so-called "cathodal escape". This phenomenon will have critical influence when studying short nerve segments as in investigating a possible proximal nerve entrapment (e.g., ulnar nerve "inching technique" in stimulation at the elbow).

Over-stimulation may also result in co-stimulation of an adjacent nerve. Fig. 12A shows a median nerve conduction study with proper stimulus levels and normal findings. When the nerve was stimulated excessively (78 mA instead of 25 mA) the wrist latency is reduced, CMAP amplitude from wrist stimulation is much higher than from elbow stimulation and the conduction velocity is reduced compared to normal (Fig. 12B). This gives an impression of neuropathy. The initial positive deflection in wrist stimulation is a clue to this technical pitfall. This error is likely to occur when a CMAP has increased latency and markedly decreased amplitude (e.g., carpal tunnel syndrome). The "compensatory" increase in stimulation intensity will result in an early positivity which should raise suspicion for co-stimulation, in addition to seeing a visible twitch in the ulnar-innervated muscle. If excess stimulation is suspected, the intensity should be noted, and slowly decreased to observe the abrupt changes in CMAP latency and amplitude where the co-activation occurred. Once this is identified, the stimulus can be adjusted down to the appropriate level for measurement.

6.9. Muscle fiber length

Changes in MF length will affect CMAP amplitude. This is seen primarily in the APB and ADM muscles in the hand. Shortening the MF by passive abduction results in higher CMAP amplitude and shorter CMAP duration: lengthening the MFs produces the opposite effect (Fig. 13A) (Hashimoto et al., 1994; Kim et al., 2005). In ulnar motor conductions, therefore, limb and hand position may alter the ADM CMAP (Fig. 13B,C). This can be avoided by having the subject's arm relaxed supine on a pillow or the exam table with the elbow flexed to about 90 degrees. This may also be relevant when stimulating proximal arm muscles, like biceps. All CMAP recordings in a nerve conduction study should be performed using the same limb and finger position. This is a minimal problem in lower extremity recordings.

6.10. Recording electrode montage

What does the montage of E1, E2, and E0 represent? E0 is not a true ground electrode, nor does it play any role in the electrical safety of the patient. E0 cancels the electrical noise and interference between it and E1, as well as between it and E2, being essential to remove the 50–60 Hz alternating current artifact (Robinson

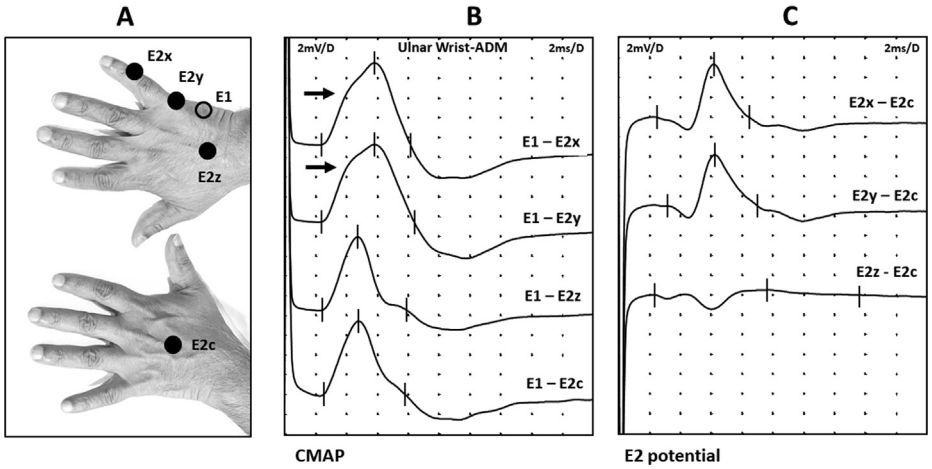
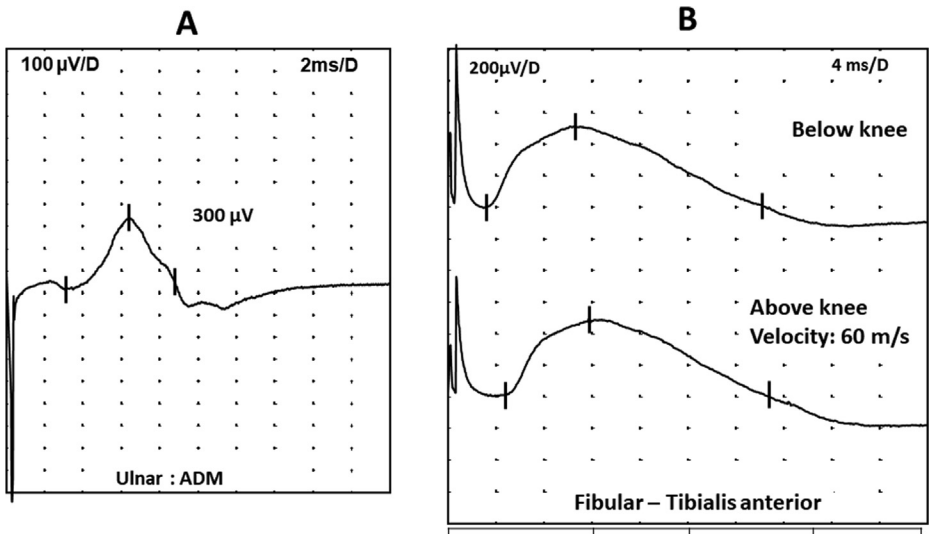


Fig. 14. Technical aspects. Effect of E2 position in CMAP (A) Filled circles indicated 3 positions of E2. Positions E2x and E2y are used in most laboratories. Position E2z is a proximal position away from the muscle. The open circle is the E1 electrode. The E0 electrode is not shown. An electrode is also placed on the contralateral hand (E2c). (B) CMAP amplitude varies due to different contributions from E2. (C) The signal recorded by E2 at different positions (using contralateral hand as reference) is similar in amplitude to the overall CMAP in the top trace. See text (6.10) for details. (with permission, S.D. Nandedkar, Ph.D.).



Site	Latency (ms)	Amplitude (mV)	Duration (ms)
Below knee	3.2	0.5	23.0
Above knee	4.7	0.5	22.8

Fig. 15. Low amplitude CMAPs. (A) Triphasic waveform recorded from a wasted muscle of a patient with motor neuron disease (B) Long duration waveforms recorded from a patient with critical illness myopathy. (with permission, P.E. Barkhaus, M.D.).

et al., 2016). Wee and Ashley reported the effect on stimulus artifacts in normal subjects using different E0 placements (Wee and Ashley, 1989). In their study, the stimulus artifact was minimal when the recording electrodes were between E0 and the stimulus site. With modern systems, placement is usually not a significant issue. It is optimally placed between the cathode and E1, closer to the former. On occasion, movement of E0 may improve signal quality. In practice, it is placed on the dorsum of the proximal hand or foot, allowing for most conduction studies to be performed without additional E0 adjustment unless artifact occurs. Occasional circumstances may occur such as in doing the needle electrode examination in the setting of significant electrical interference from a deep brain stimulator where E0 must be as close to the recording electrodes as possible (Nandedkar et al., 2013b).

E1 is placed at the center of the muscle belly, assuming it to be the end-plate region. When E1 overlies the endplate zone, the CMAP has an initially negative (upward) deflection (Dumitru et al., 2023). However, in neurogenic disorders the endplates may be distributed over an extended region (Aquilonius et al., 1984). Hence one can record waveforms with initial upward deflection at several E1 positions (Fig. 11A, B). Each position gives a different amplitude and duration. Latency also varies, but much less than amplitude (Bromberg and Spiegelberg, 1997). This amplitude variation can make CMAP comparisons difficult in longitudinal studies. E1 position should be adjusted to record the CMAP with the highest amplitude to ensure reproducibility which will also have the sharpest rising edge as originally recommended by Hodes (Hodes et al., 1948).

E2 placement should be no closer to E1 than the tendinous end of the muscle. E2 records electrical activity through volume conduction (Nandedkar and Barkhaus, 2007). To further reduce E2′s effect in the hand, it can be placed more distal on the digit (e.g., the fifth finger in an ulnar ADM or the thumb in a median APB recording). Fig. 14A,B shows the E2 recorded signal for 4 different E2 positions. E2 can contribute significant voltage to the CMAP (Brashear and Kincaid, 1996; Kincaid et al., 1993; Nandedkar and Barkhaus, 2007; Phongasmart et al., 2002). For the ulnar and tibial nerves, the average E2 contribution to the CMAP is 70 % and 83 %, respectively (Nandedkar and Barkhaus, 2007). The tibial CMAP recorded from the abductor hallucis (AH) is unique since there is a large E2 contribution to the CMAP, the result of recording all the tibial-innervated intrinsic foot muscles in addition to the small contribution from the AH (Nandedkar and Barkhaus, 2007).

E2′s contribution cannot be avoided with standard recording montages. Is E2′s contribution necessary? If E1′s contribution could be more "isolated" from E2's, then a more accurate assessment of the muscle recorded by E1 could be made. This has significant implications for its use in neuromuscular disorders and in advanced techniques such as MUNE. When E0 and E2 were placed proximal to E1, E2's influence was reduced (Fig. 14B,C, third traces) (Nandedkar and Barkhaus, 2020). Other authors have reported similar results (Day, 2020, 2021; Escorcio-Bezerra et al., 2019b). The trade-off in minimizing E2 is that the CMAP amplitude and area will be lower than in the conventional montage, particularly in ulnar and tibial nerve studies (Nandedkar and Barkhaus, 2007).

6.11. CMAP shape

Fig. 4 shows CMAPs from different muscles of a healthy adult subject. The shape of the CMAP varies from simple biphasic to irregular with extra peaks. Irregularities in a CMAP can be helpful in ascertaining that a proximally evoked CMAP matches the one that was recorded at distal stimulation. Recall that the CMAP results from the combination of two waveforms, i.e., the contributions from E1 and E2. Simple biphasic CMAPs occur when the recording electrode overlies the muscle's endplate zone and there is minimal contribution from E2, e.g., the median and fibular nerves where the E2 contribution is less prominent (Nandedkar and Barkhaus, 2007). As stated in section 6.10, E2 contributes significantly to the ADM CMAP in ulnar nerve studies, in which an extra peak or "shoulder" is often seen (Fig. 14B, traces 1 & 2, arrows). In tibial nerve studies (Fig. 4) recordings from the AH may resemble the ADM with an extra peak (dark arrows) but may also have more complexity as the contribution from E1 is minimal (about 20 %) and most of the AH CMAP reflects contributions

from all intrinsic foot muscles. (Barkhaus et al., 2011; Nandedkar and Barkhaus, 2007).

Triphasic CMAPs occur when E1 is off the motor endplate zone (Dumitru, 2023) (Fig. 11B, top trace), when there is anomalous innervation (Fig. 7A, bottom trace), or there is overstimulation of the nerve (thus co-stimulating an adjacent nerve) (Fig. 12B). In a fibular nerve conduction study (Fig. 7B), the distal stimulation recording shows an initial negative deflection. With stimulation at knee, a low amplitude slow positive phase may be seen when the display sensitivity is increased. This represents volume conducted potentials from the distal leg muscle, (e.g., tibialis anterior), that are stimulated along with the EDB muscle. This volume conducted activity is not completely suppressed by the differential amplifier. The onset marker should be placed at the onset of the negative deflection, ignoring the initial positive waveform. In some neuromuscular disorders (usually neurogenic), the muscle recorded by E1 is severely affected, i.e., wasted, resulting in minimal to absent input from E1. The CMAP is then primarily derived from E2 (and as such is a far-field potential) (Fig. 15A). This can be demonstrated by moving E2 proximal, e.g., in the hand move the E2 from the digit to the dorsum of the wrist (Nandedkar and Barkhaus, 2020).

Low CMAPs, <500 μV, should be treated with caution and those < 200 μV should be confirmed with an intramuscular needle recording. If after numerous attempts in re-positioning the E1 only a triphasic wave can be obtained in the hand muscles (Fig. 15A), we recommend moving E2 proximal to the dorsum of the wrist. Very low amplitude (<500 μV) CMAPs are of limited use in measuring conduction velocity. In very chronic processes, the SMUPs may become quite large (>1 mV). In such situations one may be measuring the conduction velocity from a single MU. One method to ascertain this is to stimulate at liminal intensity with subsequent slow increase in stimulus intensity. Identify how many increments are needed to achieve maximal amplitude. Very low amplitude CMAPs in neurogenic disorders typically have very few component SMUPs (see section 11.1).

Far-field potentials may obscure or imitate a CMAP. Clinical neurophysiologists may develop a routine of observing the display screen rather than the muscle being recorded while increasing the stimulus intensity. At high stimulus intensities, far-field responses can arise from E2 (see 7.2). For optimal recordings and in order to avoid excess stimulation, observe the muscle being studied for a "twitch" correlating to the stimulus before looking at the display screen.

6.12. Stimulus frequency

In routine neurography, single stimuli are used. In repetitive motor nerve stimulation, slow rates of supramaximal stimulation (3–5 Hz) are recommended. Successive CMAPs recorded in normal individuals should be superimposable (congruent). If variability in size or shape occurs, one should suspect technical error or a disorder of neuromuscular transmission. At higher rates of stimulation, CMAP negative amplitude may increase without change in negative area with decrease in negative CMAP duration. This potentiation is suggested to reflect stimulation of the Na/K pump (Hicks et al., 1989; McComas et al., 1994) or to result from increased MF conduction velocity (van Dijk et al., 2000), or MF shortening. This is the basis for using a low frequency repetitive motor nerve stimulation technique as to avoid this phenomenon in postsynaptic disorders (see section 10.2).

6.13. The operator

After the above discussion of technical points in recording CMAPs and performing MNCS, it is the operator, or clinical neurophysiologist, who will ultimately determine the quality of the signal. This will depend on the operator's training and experience (AANEM, 2023). The goal is to always record high-quality and reproducible signals (AANEM, 2020; Barkhaus, 2018; Kimura, 1997; Kugelberg, 1998; Stålberg et al., 2019, Neuwirth et al., 2018).

7. Biological considerations in recording the CMAP

7.1. Age

CMAP amplitudes approach adult values by age 2 years. This is in part due to the smaller electrodes necessary to record from muscles in infants (section 6.4). CMAP amplitude tends to decrease after the age of 60. This is a natural aging process associated with age-related motor neuron loss. In mature adults, the extensor digitorum brevis CMAP may (but not always) be reduced or even absent in otherwise normal individuals. Although this is usually attributed to aging, a remote history of ankle trauma may be discovered. If all other motor (including the tibialis anterior CMAP) and sensory potentials are normal and no other putative causation evident, this may be considered an isolated finding of uncertain significance (Stewart, 2010).

7.2. Anomalous innervation

The commonest anatomic variation seen is the Martin-Gruber anastomosis in which a variable number of motor axons branch from the proximal median nerve to join the ulnar nerve in the forearm. This anomaly has been subclassified into various patterns that can be readily identified by altering the recording montages (Dumitru et al., 2002; Kimura, 2013a; Stewart, 2010). Additional variations in the innervation of the intrinsic hand muscles may occur, e.g., the Riche-Cannieu anastomosis that may account for an "all ulnar hand" (Dumitru et al., 2002). Fig. 7A shows the frequently confusing situation when the patient also has carpal tunnel syndrome. The distal latency is increased as expected. On proximal stimulation, there is an initial positive deflection due to far field potentials from the ulnar innervated muscles. The latency at the first deflection is 'normal' from ulnar nerve fibers. This gives an artificially short latency difference between distal and proximal sites and hence a spurious high conduction velocity. Using the latency at the baseline crossing will give the correct velocity.

A variation may occur in the innervation of the EDB muscle by the deep fibular nerve (Fig. 7B). If the distal EDB CMAP amplitude is found to be smaller than the proximal CMAP, a stimulus should be applied behind the lateral malleolus to identify an anomalous accessory deep fibular branch via the superficial fibular nerve (Infante and Kennedy, 1970; Lambert, 1969a).

There have also been reports of anomalous innervations between the fibular and tibial nerves, but these are far field potential artifacts associated with excessive nerve stimulation. This reflects the significant contribution of E2 in tibial motor conduction studies (Amoirodis et al., 1996).

Recordings of far field responses in the fibular and tibial nerves can easily be ascertained by simple experiments (Fig. 7C). First, set up a standard montage for a distal fibular motor conduction recording from the EDB. After obtaining the CMAPs (top trace), stimulate the distal tibial nerve without changing the montage on EDB. The "CMAPs" obtained (bottom trace) are far field responses from the base of the fifth toe (E2). This pitfall is typically seen when the EDB response is absent, and the operator uses very high stimulus intensity. This maneuver can also be done in reverse: set up the tibial motor montage and record the CMAP (Fig. 7D, top trace). Then stimulate the distal fibular nerve. This will also result in a far field recording but typically requires higher stimulus inten-

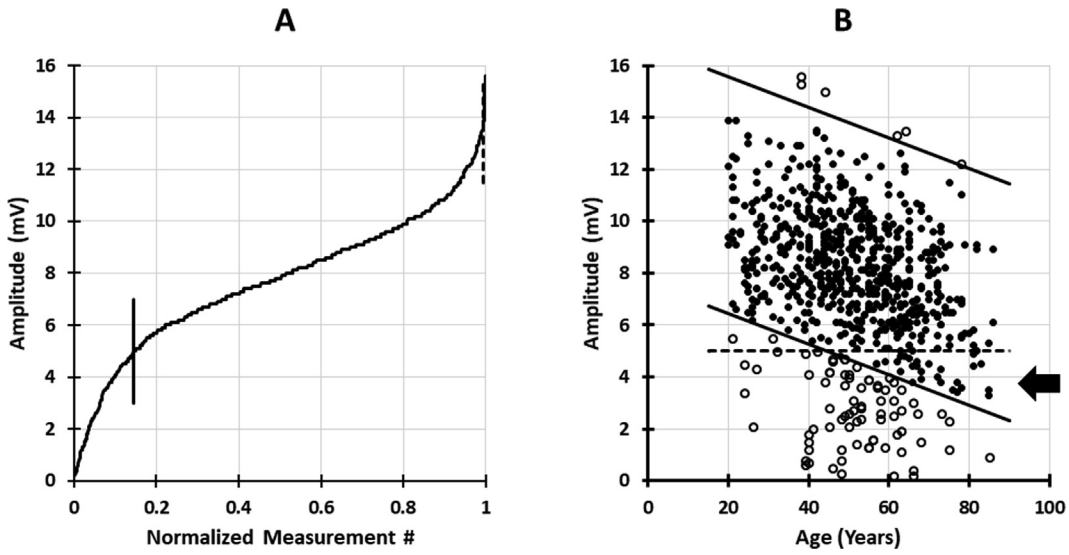


Fig. 16. CMAP amplitude from 729 ulnar motor conduction studies from subjects referred for electrodiagnostic studies were tabulated (Courtesy of Dr Mansukhani and colleagues). (A) ERef analysis gave a lower limit of 5 mV that is same as limit used in the laboratory. (B) MeRef analysis shows a strong negative correlation between CMAP amplitude and age ($r = 0.42$, $p < 0.001$). The lower limit of amplitude is less for older subjects. See text (8) for details.

sity (bottom trace) (Amoirodis et al., 1996; Brashear and Kincaid, 1996; Kincaid et al., 1993; Nandedkar and Barkhaus, 2007).

8. Reference values

Assessment of CMAP measurements requires "normal" values. These value limits are defined based on studies in presumed healthy subjects. Also, the limits are defined to include the majority (>95 %) of observations in those subjects. There is always a slight chance that a healthy subject may have CMAP measurements that are outside the "normal" limits. Hence, we prefer to use the term "reference values (RV)". Ideally, each laboratory should define their own RVs. While there is no minimum normal value for CMAP distal latency or maximum for CMAP amplitude, extreme values should raise concern for technical error.

The traditional approach is to collect data from a cohort of individuals without known neuromuscular disorders using a specified technique and montage. Many laboratories in clinical practice adopt published RVs by following the prescribed protocol used to record them. By using test settings used for collecting RVs, one can avoid technical errors in CMAP assessment. However, the RVs are also affected by patient demographics: age, height, body mass index (BMI), etc. (Chen et al., 2016). These can be different in different regions of the world. A prospective study would be ideal but is usually impractical due to lack of resources and time constraints.

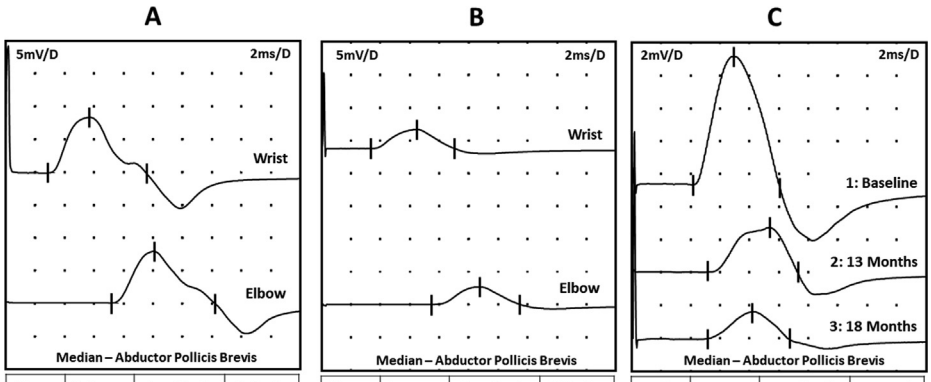
A novel approach is proposed to derive RVs from patient data recorded in the laboratory. Fig. 16 illustrates analysis of CMAP amplitude in ulnar nerve conduction studies from all adult subjects studied over several months. All data were used for analysis regardless of the subject's clinical diagnosis. The values are sorted in ascending order and plotted serially (Fig. 16A). The x axis is the observation number divided by total number of observations. The slope of the line is relatively constant in the central region. It changes significantly at the position indicated by the vertical line. That is the RV for lower limit of amplitude (5 mV) and it is identical to the limit used in the laboratory. This analysis is called E-Norm (Jabre et al., 2013) or E-Ref (Nandedkar et al., 2017).

The Multi-Variable E-Ref (MeRef) extends the analysis by including the dependence of measurements on demographic data (Fig. 16B). The amplitude values are plotted against subject's age. The dotted horizontal line is the RV obtained from E-ref

Table 1
Summary of alterations in the CMAP in various pathologies.

Finding	Strength	Latency	Amplitude	Duration	Shape
Normal	Nl	Nl	Nl	Nl	Normal (Biphasic initial –ve)
Cold limb	Nl	▲	▲	▲	Normal
Anomalous innervation *	Nl	▼	▲	▲	Triphasic initial + ve
Focal slowing *	Nl	▲	Nl	Nl	Normal
Diffused slowing	Nl	▲	▼	▲	Multiple peaks/serrations
Uniform slowing	Nl	▲	▼	▲	Normal
Conduction block *	▼	Nl	▼	Nl	Normal
Extra discharge	Nl	Nl	Nl	▲ **	Peaks in + ve phase
Partial axon loss – Immediate	▼	Nl	Nl	Nl	Normal
Partial axon loss intermediate (2–12 weeks)	▼	Nl	▼	Nl	Normal
Partial axon loss and successful reinnervation	Nl	Nl/▲	Nl	Nl/▲	Normal
Partial axon loss and incomplete reinnervation	▼	Nl/▲	Nl / ▼	Nl/▲	Normal
Severe axon loss, incomplete reinnervation	▼	Nl /▲	▼	Nl/▼	Normal
Atrophy of muscle fibers	▼	Nl	Nl / ▼	Nl / ▲	Normal
Loss of muscle fibers	▼	Nl	▼	Nl	Normal

* Stimulation proximal to site of lesion or anomalous nerve branching.
** Onset-end duration



Site	Latency (ms)	Amplitude (mV)	Velocity (m/s)
Wrist	2.9	8.5	---
Elbow	7.5	7.9	51

Site	Latency (ms)	Amplitude (mV)	Velocity (m/s)
Wrist	3.4	2.9	---
Elbow	7.5	2.7	55

Study	Latency (ms)	Amplitude (mV)	Strength
1	4.0	7.9	4+/5
2	5.6	2.7	4-/5
3	5.4	1.6	1/5

Fig. 17. CMAP waveforms (A) Normal study (B) Axon loss (C) Progressive axon loss. See text (10.1.1) for details. (with permission, S.D. Nandedkar, Ph.D.).

(Fig. 16A). The slanted lines represent the upper and lower normal limits from MeRef. Open circles indicate abnormal measurements. Any result that is greater than the upper limit of amplitude may represent a true outlier or a technical artifact (e.g., co-stimulation of nerve as seen in Fig. 12B). Note the RV is lower in older subjects. Such an approach has been used to revise RV for other CMAP measurements also (Nandedkar et al., 2021a, 2021b, 2021c).

CMAP symmetry has received relatively little attention (Bromberg and Jaros, 1998; Kothari et al., 2000; Willems et al., 2021). Using CMAP amplitude alone in symmetry measurements may be insufficient due to the large influence of E2 on the CMAP, especially in the tibial nerve (see above). In addition to CMAP amplitude, CMAP negative area should also be compared. Asymmetry of up to 50 % is considered acceptable. However, if temperature, E1 placement, and other conditions are optimal, a more conservative asymmetry of up to 25 % may be more realistic.

9. Reproducibility

CMAP reproducibility has been investigated in recent studies exploring the repeatability of different motor unit number estimation (MUNE) techniques (see section 11.1). In a single subject round-robin study involving 12 raters, several muscles were investigated (ABP, abductor digiti minimi [ADM], AH, biceps brachii, ED and TA), calculating the intra-rater and inter-rater reproducibility for the CMAP and for MUNIX (Motor Unit Number Index) calculations. Regarding the CMAP, the mean coefficient of variation (CoV) ranged from 4.2 % (ADM and ABP) to 9.9 % in TA, but this was done in an experimental setting with time provided to improve the recording quality by changing electrode (E1) position (Neuwirth et al., 2016).

In a very large study, 36 raters from 24 centers investigated the APB, ADM, biceps brachii, EDB, first dorsal interosseus, and TA muscles from 4 healthy volunteers. After careful training, the tests were repeated as necessary in order to attain a CoV < 20 %, required to accept the results. CoV mean values were about 6.5 % for the ADM, about 7–8 % for ABP, FDI and TA, 9 % for EBD and 13.5 % for the biceps (Neuwirth C, et al., 2018) In another round-robin study using the MScanFit MUNE (see section 11.1), 12 raters from 6 centers examined 6 healthy controls. The CoV for the APB was 11.1 % and for the TA 6.1 % (Sørensen et al., 2022) In a recent study using the CMAP scan technique (see section 11.1) involving 15 groups in 9 countries, intra-rater CoV for the CMAP was 12.1 % for the TA, 16.8 % for the ABP and 18 % for the ADM (Sørensen et al., 2023).

Overall, CMAP reproducibility is lower than the pre-determined ideal. However, from these studies, we can conclude that small hand muscles have a similar variability with a CoV lower than 20 %. Results from the TA and EDB are more variable, but not very different from hand muscles. Values for biceps brachii are less consistent. Furthermore, outside the ideal conditions of in a research study where training should be optimal, (Barkhaus, 2018) CoV values are likely to be higher.

It is not simple to define a cut-off value for a "physiological" change of CMAP amplitude from one test to another: possibly, a value of about 30 % should be considered acceptable in the upper extremity. In addition to the above studies, other studies of the lower limb (Davalos et al., 2023; Kim et al., 2022) suggest that 50 % may be acceptable. To optimize CMAP reproducibility and minimize variability, we reiterate the recommendation of Hodes et al. (section 6.8) that it is essential to adjust the E1 position in order to obtain the maximum CMAP amplitude response (Hodes et al., 1948). CMAP variability resulting from technical aspects of recording methods can therefore be partially corrected.

10. CMAPs in neuromuscular disorders

CMAP waveform and measurements can change in many ways in different pathologies. This is summarized in Table 1 and many commonly seen waveforms are presented in Fig. 15B and 17–21. For reference, a normal conduction study is shown in Fig. 17A. At the distal site, one observes a relatively smooth biphasic waveform of normal latency and amplitude. On proximal stimulation the CMAP is similar in shape to the distal response, with slight reduction in amplitude and area, and a slightly increased duration. The conduction velocity is normal. Examples of commonly encountered pathology appear in the following sections. We emphasize that the separation between neurogenic axonal and demyelinative disorders, etc. is not absolute, particularly in mild or early cases.

10.1. Neurogenic and demyelinating disorders

10.1.1. Axonal

In acute partial motor axon loss (e.g., traumatic partial transection of the nerve), the distal segment remains excitable for 7–10 days, depending on the length of the affected segment, following which there is a loss of amplitude depending on the number of axons/MUs lost from Wallerian degeneration. In Fig. 17B, note the reduced amplitude due to loss of axons/MUs. The waveforms

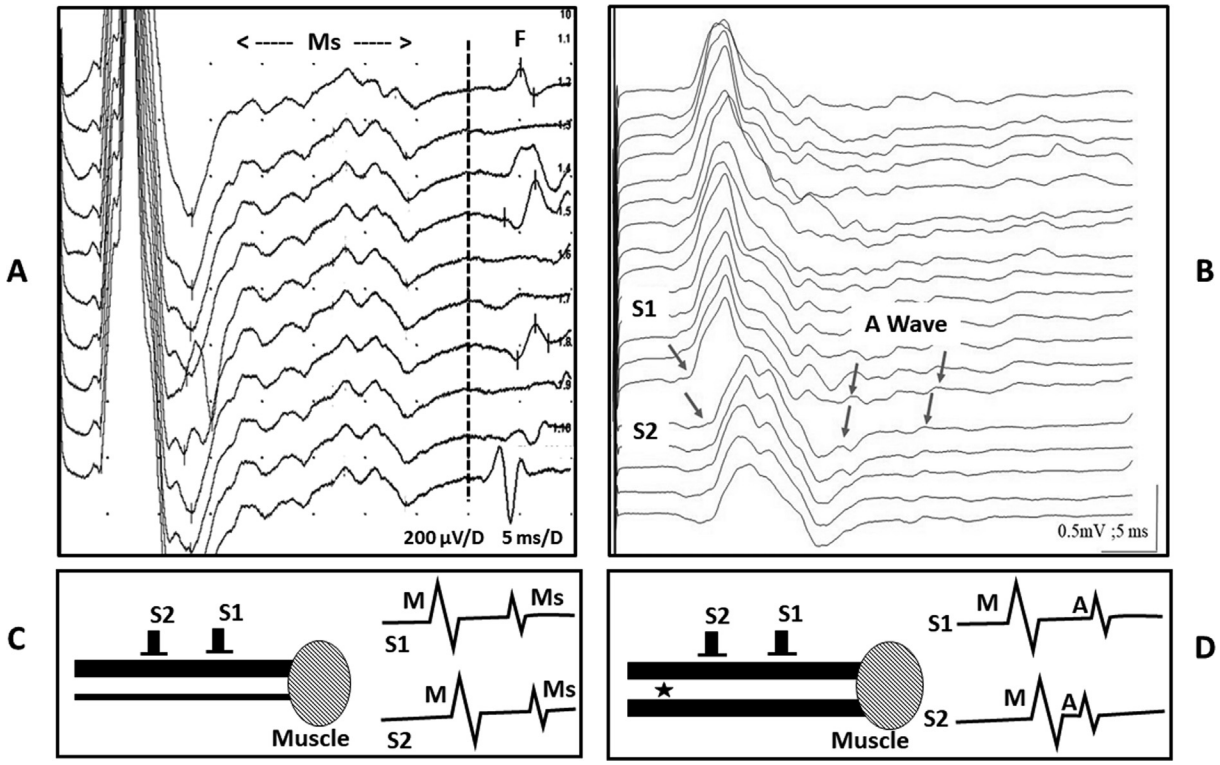
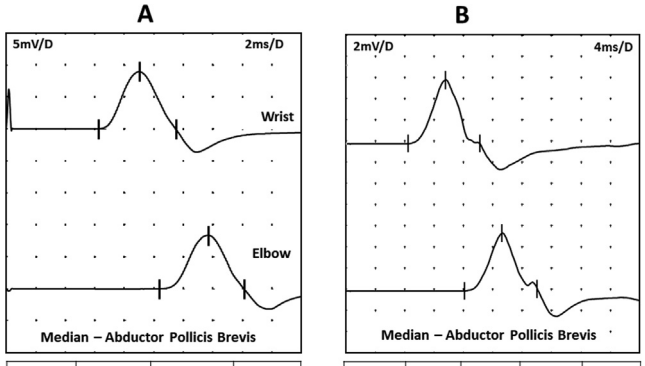


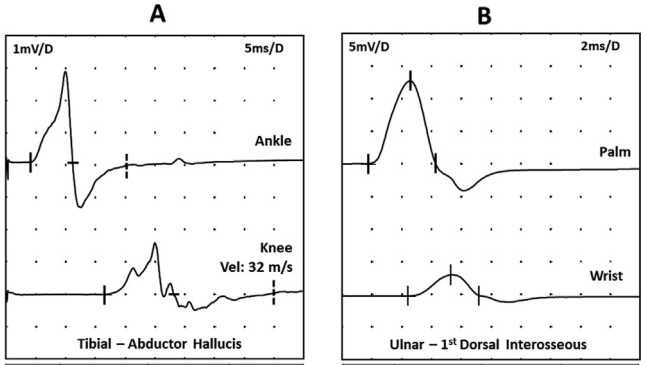
Fig. 18. CMAP Waveforms. (A) With a display setting of 200 µV/division, many time-locked potentials are seen in the return of CMAP to baseline. These are "CMAP Satellites" or "M Satellites" (Ms). They appear in a time-locked manner with each stimulation. The vertical dashed line indicate end of the CMAP. F waves are seen near the end of trace. (B) A Waves. The Ms and A wave can be distinguished by moving the stimulator slightly proximal (from S1 to S2). (C) The CMAP and Ms move right, i.e., increase in latency with proximal stimulation at S2. (D) The CMAP is delayed with S2, but the A wave latency is reduced. The star indicates the proximal location where the nerve depolarization occurred for the A wave. (with permission, E.V. Stålberg, MD., Ph.D.).



Site	Latency (ms)	Amplitude (mV)	Velocity (m/s)
Wrist	6.3	9.0	
Elbow	10.4	8.4	52

Site	Lat (ms)	Ampl (mV)	Dur (ms)	Vel (m/s)
Wrist	8.5	6.0	9.7	
Elbow	16.2	5.5	9.9	29

Fig. 19. CMAP waveforms. (A) Focal demyelination in a patient with carpal tunnel syndrome. (B) Uniform slowing in a patient with inherited polyneuropathy. See text (10.1.2) for details. (with permission, S.D. Nandedkar, Ph.D.).



Site	Amplitude (mV)	Area (mV x ms)	Duration (ms)
Ankle	2.8	8.3	7.2
Knee	1.6	5.7	11.7
Ratio	57%	69%	163%

Site	Amplitude (mV)	Area (mV x ms)	Duration (ms)
Pam	12.8	29.5	4.5
Wrist	3.2	7.7	4.8
Ratio	25%	26%	107%

Fig. 20. CMAP waveforms. (A) Increased temporal dispersion, Horizontal tick mark indicates the baseline crossing used for duration measurements of the negative peak shown in the table. The vertical dashed tick mark indicates the end of the CMAP used for measuring the total duration. It increased from 15.8 ms at ankle to 28.2 ms at knee stimulation. (B) Conduction block. See text (10.1.2)for details. Vertical tick mark is used to indicate end of negative peak. (with permission, P.E. Barkhaus, M.D.).

have normal latency, velocity and appearance indicating no conduction abnormalities.

The mechanisms of axon regrowth and collateral reinnervation allow for a variable degree of recovery. The latter mechanism is more likely to occur when there is only partial loss of motor axons supplying the muscle. Collateral sprouting and innervation of the orphaned MFs will increase the innervation ratio (i.e., number of MFs innervated by a motor axon). As the component SMUPs become enlarged, some recovery in CMAP amplitude and area will occur. In mild lesions, the CMAP size may even approximate pre-injury levels: in more severe lesions the compensatory process will only partially restore the CMAP. In very chronic processes (e.g., old polio), the CMAP amplitude may be normal even though it is comprised of only a few remaining MUs having a very high innervation ratio.

In progressive diffuse disorders (e.g., polyneuropathy, motor neuron disease), the progressive decline in the CMAP amplitude and area will generally reflect the rate of progression of disease. Fig. 17C shows a CMAP recorded from the APB muscle of a patient with amyotrophic lateral sclerosis. Note the decline in amplitude as the muscle became weaker. If progression is slow with well-compensated reinnervation, up to 30–50 % of motor neurons may be lost before clinical weakness occurs (Carleton and Brown, 1979; Wohlfart, 1957, 1958). When progression is rapid in motor neuron disease, motor axon loss exceeds the ability of the declining number of surviving axons to innervate the denervated MFs. Given ongoing denervation/reinnervation, there is instability in the neuromuscular junctions and mild decrement in CMAP may be seen on repetitive nerve stimulation (Lambert, 1969b). In slowly progressive processes, CMAP amplitude may be maintained within the normal range until the compensatory processes (including reinnervation leading to fiber type grouping, muscle fiber hypertrophy and splitting) are overwhelmed (Swash and Schwartz, 1982, 1997) at which point the CMAP begins to decline (Nandedkar, et al., 2010, Neuwirth et al., 2017). In Fig. 17C, the top trace shows a low normal amplitude response when the patient noticed the weakness. With further loss of MUs, the CMAP amplitude decreased further, at which point the muscle became weaker. Due to loss of fast conducting axons, the onset latency is mildly increased in the bottom two traces. CMAP latencies remain within normal range while CMAP amplitudes are > 80 % of the lower limit of normal. Conduction velocities are also maintained and are within 70 % of the lower limit of normal for that nerve (Bromberg, 2011).

In addition to the decline in CMAP amplitude and area, any increased variation in motor axonal diameters will result in increased temporal dispersion (see section 4) (Fig. 18A). This gives the CMAP an irregular appearance that may be missed at low sensitivity. These irregularities in the return of CMAP to baseline have been called "CMAP satellites" or "M satellites". These should not be confused with the satellite "late potentials" seen in the motor unit potentials recorded with needle electrodes; these represent potentials arising from small diameter MFs belonging to the same MU. This can lead to problems in measuring CMAP duration if there are multiple distinct components in the CMAP as opposed to small irregularities in the baseline. The satellite potentials have the same latency and waveform on successive stimulations as seen in an A wave on late response studies (Fig. 18B). The latter is considered to be a muscle potential that follows the CMAP, due to ephaptic excitation, proximal axonal branching, or focal hyperexcitability of neighboring motor axons. It is usually seen occurring between the CMAP and F wave (Dengler et al., 2020).

Satellite and A waves can be differentiated quite easily by moving stimulation site slightly proximal. Due to increased distance the CMAP waveform and the satellite will be shifted right (Fig. 18C). If the late potential is an A wave, proximal stimulation will increase the CMAP latency due to longer distance and reduce the A wave latency due to shorter distance for nerve AP propagation (Fig. 18D). Another method to differentiate the two is by double stimulation with short inter-stimulus interval.

10.1.2. Demyelination

Criteria for demyelination have been based mainly on electrodiagnostic criteria used in clinical studies, particularly chronic inflammatory polyradiculoneuropathy (Bromberg, 2011; Van den Bergh et al., 2021). In focal demyelination, as for example in carpal tunnel syndrome, the primary finding is the increased distal motor latency (DML). Abnormal temporal dispersion is not significant and hence the CMAP waveform, amplitude and conduction velocity may be normal until marked motor axonal loss occurs (Fig. 19A).

In generalized demyelinating conditions, there is slowing in the DML as well as in conduction velocity in more proximal segments. In autoimmune neuropathies conduction block is typical. In inherited processes such as hereditary sensory motor neuropathy Type I, the slowing is homogeneous with no irregularity in the CMAPs, although conduction block may be seen in CMT-lb neuropathy (Fig. 19B). In contrast, acquired processes may show asymmetry in slowing due to variable degrees of demyelination with concomitant irregularity/complexity in the CMAPs. When this is prominent, it may be difficult to differentiate phase cancellation in the SMUPs from conduction block by measuring CMAP amplitude, area, and duration between the distal and proximal evoked responses (Brown and Feasby, 1984). Fig. 20A shows a very complex waveform with significantly increased duration on proximal stimulation (knee). This is indicative of increased temporal dispersion. As shown in the model (Fig. 2), the decrease in area is less obvious than the decrease in amplitude.

Partial conduction block due to neuropraxia is easy to identify by measuring the evoked responses below and above the block. The block should be reflected by a drop in the amplitude and area of the proximal evoked CMAP with minimal change in duration

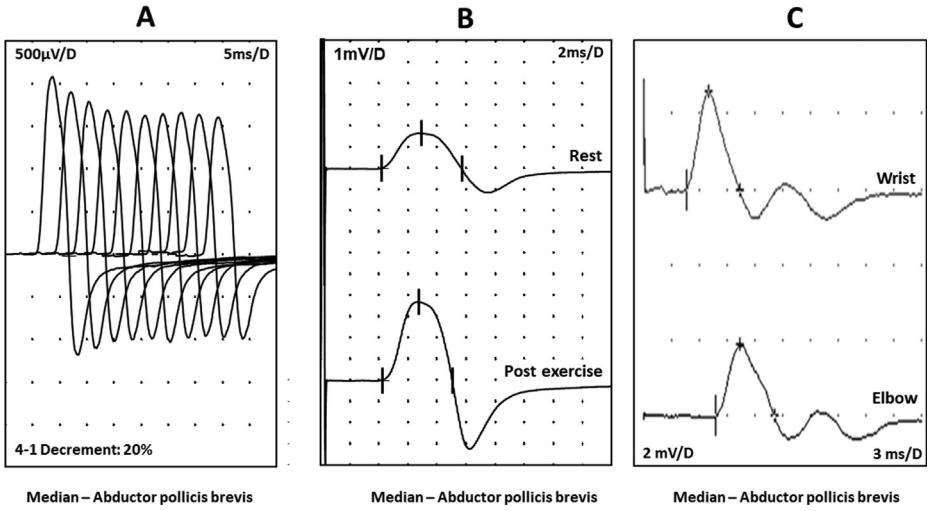


Fig. 21. CMAP waveforms. (A) Repetitive nerve stimulation shows decrement in amplitude (B) CMAP amplitude more than doubled after exercise in a patient with presynaptic abnormality. (C) Extra discharges in a patient with congenital myasthenia. (with permission, E.V. Stålberg, MD., Ph.D.).

and no irregularity in waveform. This is demonstrated in Fig. 20B. It may be helpful to stimulate at a second site just proximal to the proximal site of stimulation to ascertain that the apparent block is not due to inadequate stimulation. In simple acute neuropraxia, recovery is rapid, reaching normal values (using the contralateral unaffected muscle to compare) by about 3 months (Barkhaus et al., 2023; Gilliatt, 1980). Vasculitis (McCluskey et al., 1999) and ischemia (Barkhaus et al., 1987) may imitate conduction block.

10.2. Neuromuscular junction (NMJ) disorders

The CMAPs in these disorders vary depending on the site of abnormality at the neuromuscular junction (i.e., presynaptic versus post synaptic). What makes it more complex is that the CMAPs generated in these disorders vary in amplitude and area but not duration due to increased neuromuscular transmission time or complete block. In presynaptic disorders, the CMAPs are low normal to decreased. In severe cases of myasthenia gravis, CMAP amplitudes may be reduced due to end plate destruction outpacing new receptor replacement. This results in marked loss of MF APs to generate a CMAP. In myasthenia gravis, CMAPs often appear normal at slow rates of stimulation (<2–3 Hz). It is when neuromuscular transmission is stressed by activation (i.e., repetitive motor nerve stimulation) that abnormalities in the CMAP can be elicited (Fig. 21A). Details of repetitive motor nerve stimulation testing are beyond the scope of this review.

Presynaptic disorders have low CMAP amplitude until subjected to voluntary activation or brief high-rate stimulation. An immediate, brief, marked facilitation occurs followed by a return to baseline (Fig. 21B). Slow rate stimulation (2–5 Hz) may show a decremental response resembling myasthenia. In Lambert-Eaton myasthenia (Sanders, 2016), the facilitation is due to increased calcium influx and concentration into the presynaptic terminals where it acts as an obligatory cation in the release of the acetylcholine vesicles.

Post synaptic disorders vary in their response to dynamic testing. In myasthenia, the goal is to elicit the block in neuromuscular transmission through repetitive motor nerve stimulation. What is observed is the "macro" manifestation of the abnormal dynamics in synaptic transmission that is seen in the more sensitive testing at the "micro" level (i.e., jitter studies). What is observed as decrement in the CMAP in repetitive motor nerve stimulation is the degree of blocking seen in jitter studies. For example, let us assume that 25 % of MF pairs are blocking (i.e., the blocking occurs intermittently in association with increased jitter). Therefore, theoretically if 50 % of MF pairs block 25 % of the time, a decrement of 12.5 % in the CMAP would be expected. Increased jitter alone without blocking is not reflected in CMAP decrement. Whereas CMAP decrement due to blocking in neuromuscular transmission reflects clinical weakness, increased jitter alone may account for the fatigue in myasthenia and other related disorders.

The presence of CMAP "after-discharges" when recording a single CMAP may offer clues in abnormalities of neuromuscular transmission (Lee et al., 2016; Yang et al., 2021), . One uncommon situation is when a myasthenic patient becomes increasingly weak after taking excessive acetylcholinesterase inhibitors ("cholinergic crisis"). This results in after-discharges of the CMAP occurring immediately after evoking a single CMAP (Fig. 21C). This is due to an accumulation of acetylcholine at the receptors that desensitizes or blocks them. In a limited study, Yang et al. (2021) reported that patients with muscle-specific tyrosine kinase antibody (MuSK-Ab) positive showed a different pattern of discharges from patients who were acetylcholine receptor antibody (AChR-Ab) positive.

Congenital myasthenic syndromes may also show repetitive CMAPs following a single stimulus. In end-plate acetylcholinesterase deficiency, the repetitive CMAP responses may be quite small and are easily missed. Thus, if suspected, the waveforms should be viewed at high amplifier gain. Slow channel syndrome may show a second, smaller CMAP separated from the first CMAP by 5–8 ms, following a single supramaximal stimulus. This second stimulus will briefly disappear after voluntary activation or slow rate stimulation, recurring after a brief rest period (Engel, 2012).

10.3. Myopathic disorders

The CMAPs in myopathic disorders are typically normal because most myopathies are proximal with minimal effect on small distal muscles. In general, the CMAPs in distal muscles are usually unaffected until end stage. Reduction in bicep brachii muscle CMAP amplitude has been shown to correlate with weakness in sporadic inclusion body myositis (Barkhaus and Nandedkar, 2007).

In distal muscles, the reasons for CMAP abnormalities may be uncertain. It is important to exclude the coincidental presence of focal entrapment neuropathies. The distal myopathies are a heterogeneous group of disorders. In general, the CMAPs are unaffected in most until end stage. The needle electrode examination is critical in identifying these disorders (Dimachkie and Barohn, 2014; Udd and Griggs, 2004). Only when extensive MF loss is present will CMAP changes be expected. Since in myopathy the pathology is at the MF level, a more selective recording electrode (i.e., needle electrode) is better in detecting abnormality.

10.4. Critical illness (CI)

This is a common cause of weakness in critically ill patients, particularly those in the ICU and on a ventilator. It is frequently myopathic, but sometimes neuropathic which is inherent in the term "critical illness". Although this term is scientifically correct, it is awkward. The various abnormalities causing in CI express themselves in different ways, e.g., MF membrane instability, MF necrosis seen as fibrillation potentials, or loss of myosin. There are also signs of prolonged muscle membrane depolarization manifesting as marked prolongation in CMAP duration (Fig. 15B) (Bolton, 2005; Goodman et al., 2009; Z'Graggen and Tankisi, 2020).

In one study (Marrero et al., 2020), it was concluded that conventional electrophysiological methods can confirm the peripheral origin of acquired quadriplegia in ICU patients, but do not reliably distinguish between neurogenic vs. myogenic origins of paralysis. Sensory responses cannot help differentiating between myopathic versus neurogenic etiology. Fibrillation potentials may be seen in both. Methods for comparing direct vs. indirect muscle stimulation and refractoriness represent attractive potential diagnostic methods, but they are time-consuming, technically demanding, and the precision of CI myopathy diagnosis is questionable (Rich et al., 1997). However, decreased indirect vs. direct muscle stimulation was found to strongly suggest a neurogenic lesion (Rich et al., 1997). The hallmark of CI myopathy, preferential loss of myosin, is a major putative cause of weakness in CI myopathy patients. The myosin content can be reliably evaluated in small samples obtained with a micro-biopsy instrument (Llano-Diez et al., 2012). Goodman et al. proposed diagnostic criteria of CMAP durations of > 8 ms in the distal muscles and > 15 ms for the tibialis anterior muscle (Goodman et al., 2009).

10.5. Muscle disuse atrophy

In a large muscle atrophy syndrome, it is possible that the cross-sectional area of the muscle within the uptake area of the recording surface electrode may not decrease much (Fig. 3). Hence the CMAP amplitude in large muscles may not decrease significantly

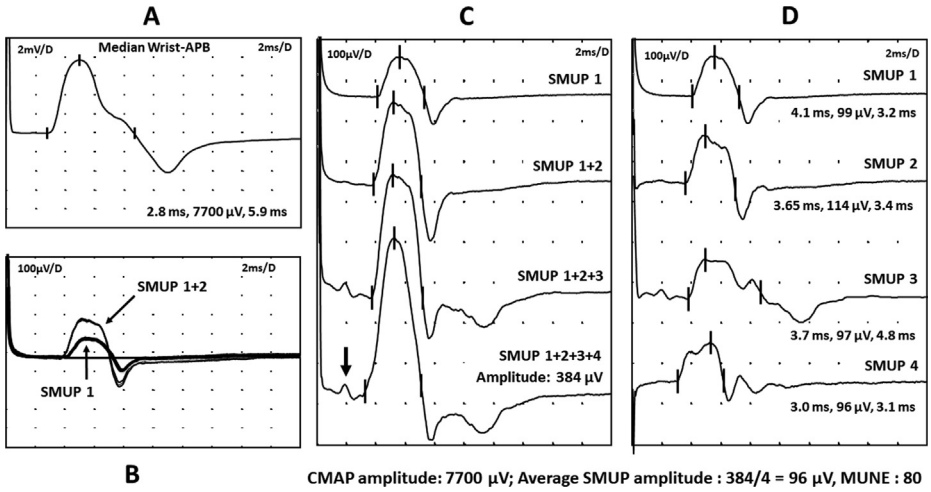


Fig. 22. Incremental stimulation of motor unit number estimation. (A) Compound muscle action potential (B) Stepwise change in response when stimulus intensity is increased. Several responses are superimposed. (C) Signals from 4 steps are shown and used to calculate the average amplitude of the surface motor unit potential. This is divided into CMAP to calculate MUNE (D) Top trace in C and D are the same and are the SMUP of the first stimulated motor unit. The difference between the second and first trace in C is shown on the second trace in D, and so on. Note the difference in waveform latency and amplitude. (with permission, S.D. Nandedkar, Ph.D.).

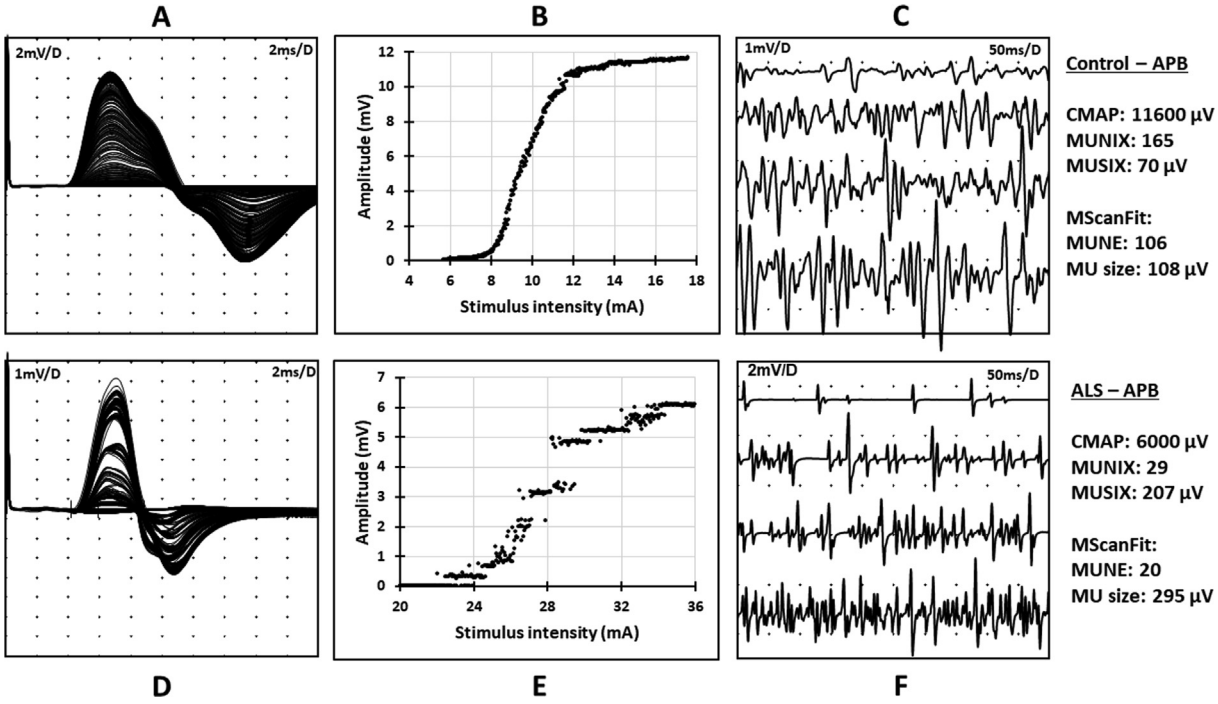


Fig. 23. Motor unit number estimation. The top and bottom row show recordings from a healthy subject and a patient with amyotrophic lateral sclerosis (A, D). Compound muscle action potential (B, E) CMAP scan (C, F) Surface EMG interference pattern at different force levels. See text (11.1) for details. (with permission, S.D. Nandedkar, Ph.D.).

when muscle atrophy is present. If small (e.g., intrinsic hand) muscles are prevented from activation (e.g., a hand that has been immobilized following a bone fracture), the CMAP decreases in amplitude and area, likely due to induced MF atrophy (Mobach et al., 2020). In contrast to CI myopathy however, CMAP duration remains normal. Once the muscle can resume normal activity, CMAP amplitude and area increase by 6 weeks, although not to normal, based on comparison with the unaffected hand. The latter may be explained by the limited time of follow up (Mobach et al., 2020).

11. Advanced techniques using CMAPs

11.1. Motor unit number estimation (MUNE) and Neurophysiological Index (NI)

In progressive motor neuron diseases such as amyotrophic lateral sclerosis (ALS), there is a loss of MUs. The number of MUs would be a useful biomarker to assess progression and response to treatments. Since the CMAP contains the SMUPs of the MUs (see Section 3), it is logical to analyze the CMAP waveform to

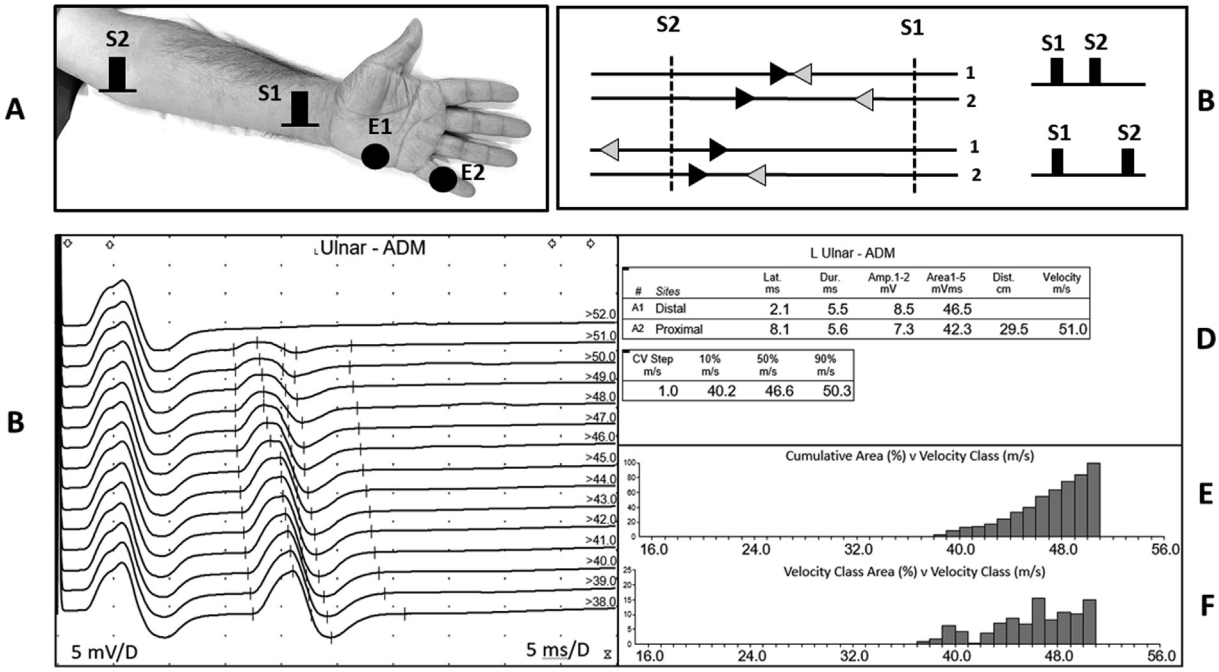


Fig. 24. Collision technique to study conduction velocity distribution. (A) Ulnar nerve is stimulated at wrist and above elbow. (B) Schematic to demonstrate collision in fast and slow conducting axons. (C) Traces recorded when the inter-stimulus interval was increased. (D) The first table shows conventional measurements of the conduction velocity. The second table shows the statistics of velocity spectrum shown in F. The cumulated distribution of velocity from smallest to highest values is shown in E. See text (11.2) for details. (with permission, S.D. Nandedkar, Ph.D.).

estimate the number of MUs. In these conditions the CMAP amplitude cannot be used as a marker for number of axons since collateral reinnervation will increase amplitude for a given number of axons. No technique purports to offer an absolute MU count. The CMAP is the quintessential signal in all MUNE methods (de Carvalho et al., 2018; Doherty and Brown, 2002; McComas, 1991; McComas, 1995).

The first MUNE method (“incremental”) was proposed by McComas and colleagues (McComas et al., 1971; McComas, 1991). They recorded the CMAP and measured its amplitude (Fig. 22A). Next, the nerve was stimulated by gradually increasing intensity. Progressive stimulation of single axons produces a stepwise change in the response (Fig. 22B). Several such steps were recorded, and the largest amplitude signal was divided by the number of steps to estimate the mean SMUP amplitude (Fig. 22C). Dividing the mean SMUP amplitude into the CMAP amplitude gave the MUNE. The concept is quite simple but was challenging in application due to lack of automation and other pitfalls, including those described in this review. Digital Subtraction of the consecutive steps gives individual SMUPs (Fig. 22D). Note the SMUPs have different onset latency (Fig. 22D) just as shown in the schematic in Fig. 1B. The negative peak duration of SMUPs is 3–4 ms whereas CMAP duration is longer at 6 ms due to temporal dispersion (see section 4.3). Also note that these APB SMUPs are shorter in negative duration compared to those from the biceps (10 + ms) due to shorter MF length (section 5).

Recent MUNE methods use computer modelling rather than direct measurements of SMUPs. In the CMAP scan method, stimulus levels that give minimal (liminal) and maximum (supramaximal) responses are measured to establish the stimulus range where CMAPs would be recorded in a decremental manner (Bostock, 2016). The nerve is stimulated 500 times to cover this stimulus range in equal steps. In a normal muscle, one observes a gradual decrease in amplitude with decreasing intensity (Fig. 23A). This is analyzed from the plot of amplitude versus stimulus intensity (Fig. 23B) using a calculation called “MScanFit MUNE” (Bostock, 2016). In normal muscle, the plot has a smooth sigmoidal shape. STEPIX is a variation of this MUNE method for analyzing this plot (Nandedkar et al., 2022).

A more widely used method is called ‘Motor Unit Number Index (MUNIX) (Nandedkar et al., 2010; Nandedkar et al., 2018; Nandedkar et al., 2019; Neuwirth et al., 2017). After obtaining the CMAP in the tested muscle, MUNIX uses the surface EMG interference pattern (SIP) signals to analyze the SMUP’s properties. The SIP is recorded at various force levels ranging from slight to maximum, which requires patient cooperation (Fig. 23C,F). MUNIX reflects the relative number of MUs in the muscle and is expressed as an “index” (it is not an absolute count just as in other MUNE methods).

Dividing MUNIX into the CMAP amplitude gives the Motor Unit Size Index (MUSIX) that reflects the degree of reinnervation in the component SMUPs. Given the variable rates of progression in motor neuron disease and related disorders, this offers the advantage of detecting an affected muscle (i.e., MU loss with compensated reinnervation) before clinical weakness is apparent (Carleton and Brown, 1979; Neuwirth et al., 2017).

MUNIX offers the advantage of speed as it takes less than 5 min per muscle by an experienced examiner. As minimal stimuli are required to obtain a CMAP followed by variable levels of voluntary activity, patient tolerance in testing is high. It is also possible to study larger muscles (e.g., tibialis anterior and biceps brachii).

These MUNE methods and others give different numerical results for the number and size of MUs reflecting the assumptions and simplifications of each model. Nevertheless, they show similar patterns. Recordings in Fig. 23D-F in a patient with ALS demonstrate stepwise decrease with gaps in the CMAP due to the reduced number of MUs and their large amplitude SMUPs (from reinnervation). The SIP signals show discrete SMUPs of high amplitude. Both methods indicate reduced number of MUs and increased MU size.

Regardless of the MUNE method, it is important to record the CMAP with maximum amplitude. Suboptimal CMAP will give a reduced number and/or size of MUs, thus making it difficult to follow any MU loss and effects of reinnervation. After our initial trials

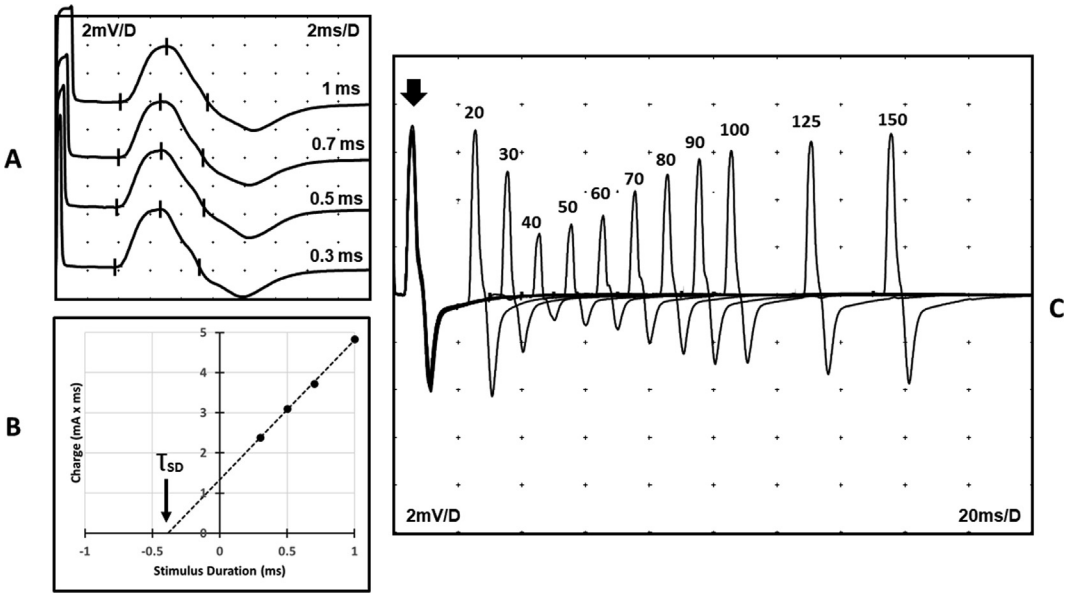


Fig. 25. Excitability testing. (A) The median nerve was stimulated, and signals were recorded from the abductor pollicis brevis muscle. The target signal had 50% amplitude of the CMAP recorded at supramaximal intensity. (B) Plot of charge versus stimulus duration is used to calculate strength-duration time constant, τ_{SD}. (C) Paired stimulation of the median nerve at wrist. The response is recorded from the APB. Traces are superimposed. The first response (indicated by arrow) is from the "conditioning" stimulus and is constant for all trials. The response from "test" stimulus decreased due to sub-excitability and recovered when the interstimulus interval (indicated above the response) was increased. The stimulus artifact from the test stimulation was digitally removed in this illustration for better visualization of the response. See text (11.3) for details. (with permission, SD Nandedkar, PhD).

in MUNIX, the importance of maximizing the CMAP amplitude for reproducibility became clear, echoing the recommendation for doing this in the first motor conductions studies in humans (Hodes et al., 1948).

If automated MUNE methods are not available, one can summate the CMAP amplitude from several muscles. The sum, called Cumulative Muscle Index (CMI), can also be used to follow the disease progression (Nandedkar et al., 2015).

The CMAP amplitude can also be used in another novel measure, the Neurophysiological Index (NI). This is a simple formula that uses conventional EMG features, i.e., CMAP x F-wave frequency/distal motor latency, to estimate the number of functional MUs in the hand muscles of ALS patients (de Carvalho and Swash, 2000; Swash and de Carvalho, 2004). The NI tends to decline during disease progression. This is due to the decrease in numbers of F-waves and increase in the distal motor latency, associated with progressive CMAP amplitude decline (de Carvalho et al., 2005). Both MUNIX and NI are more sensitive than clinical assessment for detecting MU loss in pre-symptomatic limbs of patients with slowly progressive ALS (Escorcio-Bezerra et al., 2019a). NI decline is similar in different ALS phenotypes (Cheah et al., 2011) and is a predictor of survival (Cao et al., 2019).

11.2. Conduction velocity distribution

Demyelination affects the CMAP waveform by variation in size and propagation velocity in the motor axons. This can be investigated using the collision method illustrated schematically (Fig. 24A,B) using a fast and slow axon (labelled 1 and 2 respectively). The recording electrodes are over the ADM. The nerve is stimulated at the wrist. This produces an orthodromic volley of APs that propagates to the muscle producing the CMAP. The nerve APs also propagate antidromically towards the proximal stimulation site. If the proximal stimulation is applied simultaneously or with a very short delay after the distal stimulation, the nerve AP from the proximal stimulation will collide with antidromic APs from the distal site. Hence no CMAP will be recorded due to proximal stimulation. As the inter-stimulus interval (ISI) is increased, fast antidromically propagating APs will pass the proximal site and the nerve fibers will repolarize before the proximal stimulation (axon # 1). This axon will be excited from proximal stimulation and produce a low amplitude response following the CMAP from distal stimulation. Fig. 24C shows study from a healthy subject. The top trace is recorded when the ISI is very short and only the CMAP from distal stimulation is observed. As the ISI is increased, slower conducting nerve fibers will also contribute to the second response. Hence, it grows in amplitude as the ISI s increase. Thus, one can investigate the range of conduction velocities in the nerve fibers (Fig. 24 D-F) (Ingram et al., 1987). Though commercially available in an automated program, this method is not widely used (Dorfman, 1984; Ni et al., 2020; Schulte-Mattler, 2006).

11.3. Nerve excitability

If the motor nerve fibers lose excitability, the nerve action potentials will fail to reach the muscle and result in weakness. One such failure is seen as a 'conduction block' that is discussed earlier (see 10.1.2). In other pathologies, the nerve excitability is assessed from CMAP waveforms recorded using different stimulation protocols (Kiernan et al., 2000). Excitability testing is uncommonly used in routine electrodiagnostic studies.

In the strength duration curve analysis, the stimulus intensity required to record a target response is measured at different stimulus duration settings (Fig. 25A). The charge transferred during stimulation is the product of intensity and duration. The charge shows a linear relationship with the stimulus duration. The point where the regression line crosses the abscissa is called the 'strength duration time constant' (Fig. 25B). It is related to membrane properties in the resting and active state Mogyoros et al., 1996).

Excitability is also studied using the "paired stimulation" approach (Kimura, 2013b). The nerve is stimulated twice at a single site and the response is recorded from a suitable muscle innervated by the nerve. The two stimuli are also described as the "conditioning" and the "test" stimulus, respectively. In Fig. 25B, each trace begins with the delivery of the conditioning stimulus. The response to this stimulus is constant in all trials as seen from the superimposed traces. After the stimulation, the nerve excitability goes through three states. This is studied by analyzing the response to the 'test' stimulus. At very short ISI the nerve is in a relative refractory state. With slightly higher ISI, the nerve shows super-excitability. This is followed by sub-excitability and eventual return to the baseline state. Traces in Fig. 25C illustrate the sub-excitable state and recovery. In this recording the stimulus parameters were identical for both stimuli. This protocol is called "recovery cycle".

One can also modify the intensity, duration, and polarity (depolarizing versus hyperpolarizing) of each stimulus separately. This type of analysis is not practical using manual adjustments of stimulus parameters. Systems have been developed to automate the recording and analysis technique. The so-called Trond protocol automates multiple analyses such as 'threshold electrotonus', 'current-threshold relationship', etc. (Bostock et al., 1998). This may promote the use of excitability testing in clinical use. Excitability testing has been used for research in a variety of pathologies (Kiernan et al., 2020).

12. Summary

The CMAP was the first peripheral electrophysiological signal to be clinically used in ENMG. Since its first description, it has evolved significantly from a simple, basic waveform considered of little interest to our current understanding of its complexities. This began in the 1990s, prompted by renewed interest in MUNE, in addition to digitization of signals. The latter allowed the deconstruction of waveforms, allowing better understanding of its component SMUPs and the influence of E2 and far field potentials. Because of its noninvasive nature and that it is easily tolerated by most subjects, it continues to hold great appeal for further research in expanding its use both in the clinic and in research.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure

The second author is an employee of Natus Medical Inc. No author has a competing or conflict of interest to disclose.

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