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The Electrodiagnosis of Neuropathy: Basic Principles and Common Pitfalls

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Nerve conduction studies and needle electromyography (EMG) are critical tools for diagnosis and research in patients with neuropathy, but the proper performance and interpretation of these methods remain of paramount importance. In this article we review the basic principles of these techniques and their clinical application to neuropathy, with a special focus on potential sources of error and how to avoid them.

Basic principles

Sensory and motor nerve conduction studies

Nerve conduction studies measure the strength and speed of impulses propagated down the length of a peripheral nerve. During nerve conduction studies, an action potential is triggered at a specific point along the nerve using a bipolar stimulator placed on the skin surface. The intensity of stimulation is increased from zero to a level just above that needed to depolarize all the axons within the nerve (a supramaximal stimulation) to ensure full activation. The action potentials of these axons travel together down the nerve to the recording site, where they generate a summated waveform. For sensory nerve conduction studies, the recording electrodes are placed on the skin directly over the nerve (usually over a pure sensory branch) at a fixed distance from the stimulation site (Fig. 1), where they record a sensory nerve action potential (SNAP) waveform (Fig. 2). The electrical strength of the impulse, which reflects the number of axons successfully

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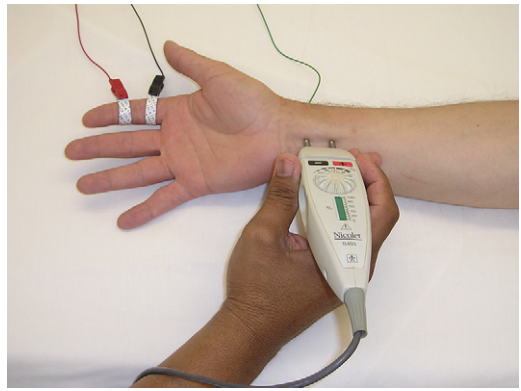

Fig. 1. Sensory nerve conduction studies of the median nerve. The bipolar stimulator is placed over the course of the median nerve at the wrist, whereas the active and reference recording electrodes are placed over the course of the median pure sensory branches in the index finger, which ensures that only sensory nerve responses are recorded. The ground electrode is placed over the dorsum of the hand.

activated (all the axons in a single nerve are activated by this technique in a normal subject), is reflected in the amplitude of the waveform, which is measured in microvolts for sensory waveforms. The speed of transmission is reflected in the latency, which is the time between stimulation of the nerve and recording of the waveform, measured in milliseconds. By also measuring the distance between the stimulating and recording sites, the latency can

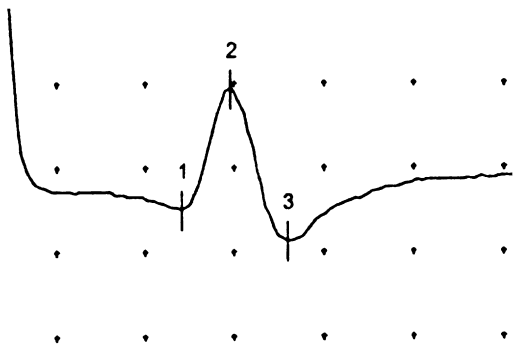

Fig. 2. SNAP generated by the setup in Fig. 1. The horizontal space between two dots (graticules) is one division and indicates time in milliseconds, which enables measurement of latency. This display value is called the sweep speed (set to 1 msec/division here). Vertical divisions indicate the strength of the potential. This display value is called the sensitivity or gain (set to 10 μV/division here). The time between the stimulus artifact and the peak of the SNAP waveform (the sensory latency) is 2.75 msec in this study, and the peak-to-peak height of the waveform (the sensory amplitude) is 13.2 μV, both of which are within the normal range for control subjects.

be used to calculate a nerve conduction velocity, another measure of conduction speed. Motor nerve conduction studies are performed in a similar fashion, except that the recording electrodes are placed over an innervated muscle (rather than the nerve itself) to ensure that a pure motor response is recorded (Fig. 3).

Each individual motor axon within a nerve supplies its own population of muscle fibers within an innervated muscle (and each axon and its muscle fibers comprise a motor unit). In a normal subject, activation of all the axons within a nerve causes depolarization of all the muscle fibers in the muscle innervated by that nerve. This summated muscle potential is then recorded as a waveform, the compound motor action potential (CMAP) (Fig. 4). The CMAP is an order of magnitude larger than the SNAP because of the high electropotency of muscle and is usually reported in millivolts rather than microvolts. Latency is not as accurate a measure of the speed of conduction in motor nerves because of the variability introduced by transmission across the neuromuscular junction to the muscle from which the response is recorded. Consequently, velocity measures are used and calculated in such a way as to factor out the effects of neuromuscular junction transmission [1–3].

The amplitude of the generated waveform and the speed of nerve conduction provide important information regarding nerve function. Waveform amplitude usually correlates best with axonal integrity, whereas conduction velocity depends highly on the degree of myelination because of the advantages provided by salutatory conduction. Consequently, loss of amplitude suggests axonal loss or dysfunction, whereas slowing of conduction velocity or latency prolongation usually implies demyelination. Focal demyelination at a single site between the simulation and recording electrodes (as with

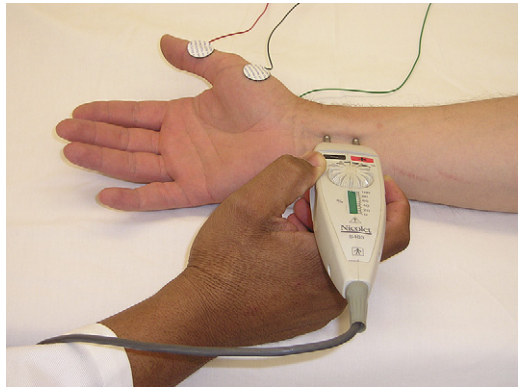

Fig. 3. Motor nerve conduction studies of the median nerve. The bipolar stimulator is placed over the course of the median nerve at the wrist, whereas the active recording electrode is placed over the median-innervated muscles in the thenar eminence, with the reference placed over a neutral distal point.

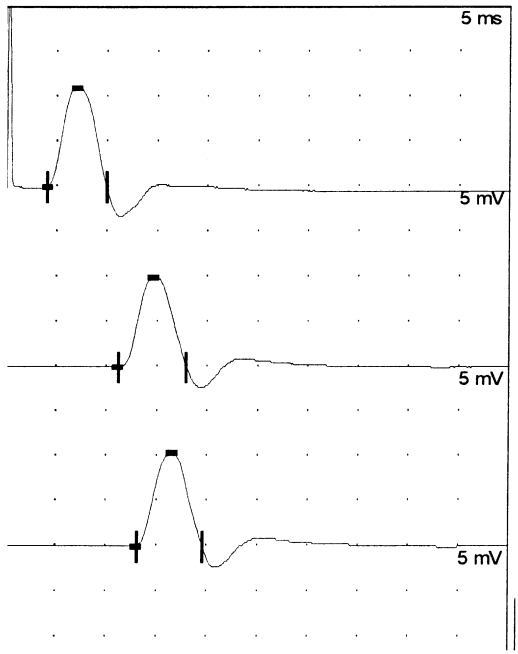

Fig. 4. CMAP. These responses were recorded from the extensor digitorum brevis muscle of the foot following stimulation of the peroneal nerve. The top waveform was recorded after stimulation at the ankle, the middle waveform after stimulation below the knee (inferolateral to the fibular head) and the bottom waveform after stimulation at the knee (in the popliteal fossa). The sweep speed is 5 msec/division and the sensitivity is 5 mV/division. These waveforms have onset latencies of 4.0, 11.1, and 13 msec, respectively (corresponding to the increasing distance between the stimulating and recording electrodes at each of the stimulation sites). Conduction velocities (calculated using latency and inter-electrode distances) are 46 m/sec for the proximal and distal segments of the nerve, whereas the amplitudes are 11.5, 10.4, and 10.2 mV, respectively, all of which are within normal limits.

entrapment neuropathy) may be severe enough to cause complete block of transmission in a substantial number of axons within the nerve, however. When this occurs, the strength of the impulse (which is the sum of the total number of activated axons within the nerve) is significantly degraded at the site of focal injury. Waveform amplitude falls as the impulse passes over the site of injury, and this loss of amplitude is proportionate to the percentage of motor axons blocked, like decreased water depth in a river downstream from a dam. This phenomenon, known as conduction block, is an important diagnostic feature of most acquired demyelinating neuropathies and is identified by comparing the waveform amplitude recorded from a nerve segment above or below a site of injury to that recorded with the injured segment between the stimulating and recording electrodes (Fig. 5).

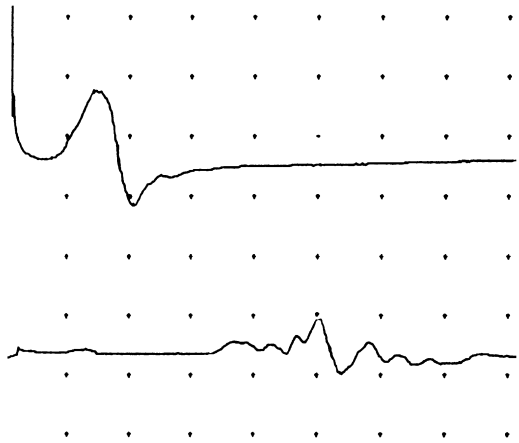

Fig. 5. Conduction block with temporal dispersion. These CMAPs were recorded from a patient with demyelinating neuropathy over the abductor hallucis muscle of the foot after stimulation of the tibial nerve at the ankle (*top waveform*) and the knee (*bottom waveform*). The sweep speed was 5 msec/division and the sensitivity was 1 mV/division. When the waveform recorded after stimulation at the ankle is compared with the waveform recorded after simulation at the knee, a dramatic 54% drop in amplitude (from 1.1 to 0.5 mV) is seen. Waveform duration also increases with concurrent increases in waveform complexity. These findings suggest demyelination of the nerve between the stimulation sites, with block of conduction in most motor axons, along with increasing variability in the range of axonal conduction times causing increased waveform duration (temporal dispersion).

The precise degree of amplitude loss needed to confirm conduction block remains controversial and may vary from nerve to nerve. For research purposes, amplitude drops of 50% over a tested nerve segment (in a properly performed study) are considered diagnostic of conduction block and strongly suggest focal demyelination or axonal ischemia [1–5]. Temporal dispersion occurs because conduction velocities differ between individual motor and sensory axons of varying size and other factors; some dispersion is normal. Over a longer distance this difference is magnified, and signals from each of the individual axons within a stimulated nerve arrive at the recording electrodes at different times. This dispersion of arrival times generates the rising and falling phases of the recorded waveform and is reflected primarily in its duration. Sensory axons demonstrate considerably more dispersion than motor axons. With loss of myelin in a nerve, temporal dispersion can increase dramatically and serves as a marker of demyelinating injury.

Late responses

Routine nerve conduction studies are limited to accessible (ie, superficially located) nerve segments in the arms and legs. Direct stimulation of

the deep proximal nerves and the nerve roots is technically challenging and often unreliable. Consequently, long latency reflex tests or late responses are typically used to assess these segments. When a stimulus is delivered to the distal nerve, action potentials are propagated both proximally and distally. The impulse traveling distal to proximal up the motor axons (in a direction opposite to the normal flow, or antidromic) eventually reaches the anterior horn cell pool, depolarizing one or a few anterior horn cells. Thus activated, these anterior horn cells then each generate small action potentials that travel back down their axons to the muscle (this time in the direction paralleling the normal flow of motor impulses, or orthodromic), activating a small portion of the muscle. A recording electrode over the muscle then registers a waveform known as the F wave (so named because it was originally recorded from the intrinsic muscles of the foot) (Fig. 6). The time required for this round trip up and down the motor nerve is measured as the F wave latency.

Although pathology at any point along the nerve can prolong the F wave latency, if normal function of the distal nerve has been documented by routine motor nerve conduction studies, F wave latency prolongation must be caused by slowing in the proximal segment of the nerve or its roots. F wave testing has limited sensitivity, however; a single normal axon may generate a normal response because the single fastest response in a group of F wave is

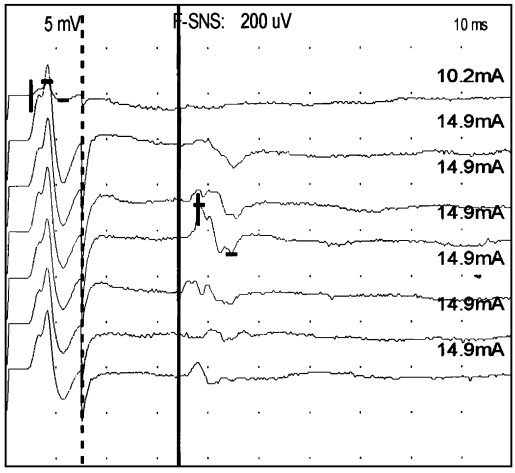

Fig. 6. F waves. This group of F waves was recorded from the thenar eminence after repeated median nerve stimulation in a patient with cervical radiculopathy. The screen is split: lower sensitivity (5 mV/division) recordings to enable display of the full initial CMAP amplitudes are to the left of the dotted line, and higher sensitivity (200 μV/division) recordings are to the right of the dotted line for clear display of the much smaller F wave responses. The sweep speed is 10 msec/division. The darker vertical line marks the onset of the earliest F wave latency in the group. This F wave latency was slightly prolonged at 34 msec because of the patient's C8 radiculopathy.

used (by convention) to measure the minimum latency and compared with normative data tables. Consequently, F wave testing is most meaningful when abnormal, and a normal F wave study does not exclude neuropathy or focal nerve injury. A different long latency response, the H reflex (named after Hoffman, who first described it in 1918) can be elicited in the legs by electrical stimulation of the IA sensory nerve afferents in the tibial nerve at the knee, triggering an ankle jerk reflex (a monosynaptic stretch reflex), with recording over the soleus muscle in the calf. H reflexes are normally recordable only from a limited number of muscles. Clinically, they aid primarily in diagnosing S1 radiculopathy and provide one of the few methods of assessing sensory and motor nerve root function [1–4,6,7].

Needle electromyography

Needle EMG plays a more limited role in the evaluation of neuropathy but remains important during initial diagnostic evaluation to exclude potential clinical mimics (eg, anterior horn cell disease, radiculopathy, myopathy). During this portion of the examination, a needle recording electrode is placed directly into the selected muscle, which is then voluntary contracted by the patient (rather than activated by electrical stimulation). Normal, full voluntary contraction of a muscle requires activation of the cortical motor strip, followed by descent of impulses down the upper motor neuron pathway and spinal cord to the anterior horn cells of each motor axon. Action potentials generated in the motor axon are propagated down the nerve to the neuromuscular junction, where electrochemical transmission activates the contraction cascade in each individual muscle fiber. A single motor axon, all of its branches, and all of its innervated muscle fibers comprise the motor unit, and the strength of a muscle contraction is determined primarily by how many motor units are simultaneously activated and how fast they are repetitively firing. The recording characteristics of the EMG needle electrode enable live recording and analysis of individual and aggregate motor unit waveforms.

During needle EMG, five core parameters are measured: insertional activity, spontaneous activity, motor unit configuration, motor unit recruitment, and the interference pattern. Increased insertional activity (the burst of activity generated by needle movement through the muscle) is a hallmark of denervation, although it also may appear with muscle fiber irritation from some myopathies. Spontaneous activity represents the spontaneous depolarization of muscle fibers while the muscle is at rest (manifested by fibrillations and positive sharp waves), without activation by their motor axons. Spontaneous activity does not occur in normal subjects and is a staple feature of active denervation caused by injury of the motor nerve or its roots, although it can, much less commonly, be caused by irritative myopathies (eg, polymyositis) (Fig. 7). Assessment of the waveform generated by motor unit activation (the motor unit action potential [MUAP]) also yields

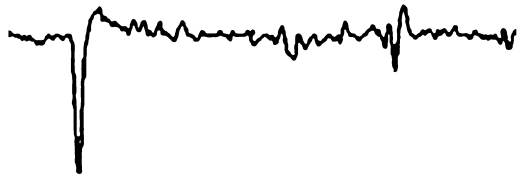

Fig. 7. Spontaneous activity. This waveform was recorded during needle EMG from the triceps muscle of a patient with cervical radiculopathy. A positive sharp wave (named after its sharp initial positive [downward] deflection) is on the left, whereas a smaller triphasic fibrillation is on the right. These markers of active denervation result from the spontaneous depolarization of denervated single muscle fibers.

important information (Fig. 8). When muscle fibers lose their innervation because of death of the motor axon supplying them, surviving motor axons in the same nerve branch to reinnervate these newly orphaned fibers in a process known as collateral reinnervation. Collateral reinnervation gradually recovers detached muscle fibers, but this process takes several months. As a consequence of collateral reinnervation, the average number of muscle fibers supplied by each axon increases, which creates larger MUAP waveforms that have longer duration, higher amplitude, and increased complexity (neurogenic MUAPs). These neurogenic MUAPs are markers of chronic motor axon injury (Fig. 9). When enough motor axons are lost or fail to transmit their action potential to the muscle, visible gaps appear in the interference pattern of overlapping MUAP waveforms normally generated when all the motor units in a muscle fire together during maximal voluntary contraction. This phenomenon is known as an incomplete interference pattern (Fig. 10). Loss or failure of the motor axons also alters the rate at which additional motor units are activated (or recruited) as voluntary contraction is ramped up from zero to maximum, which produces an

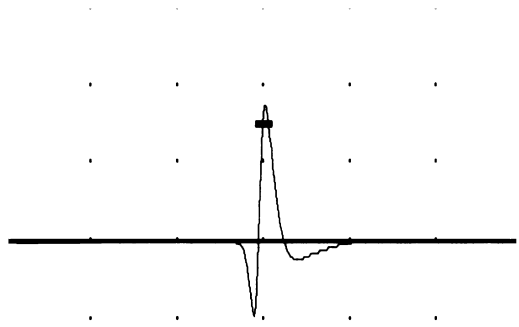

Fig. 8. Normal MUAP. This waveform was recorded by a concentric needle electrode from the biceps muscle. It was the first potential recruited during minimal voluntary contraction in a normal subject. Sweep speed is 10 msec/division, and sensitivity is 500 μV/division. This waveform amplitude is 1.4 mV, its duration is 12.5 msec, and its morphology is normal.

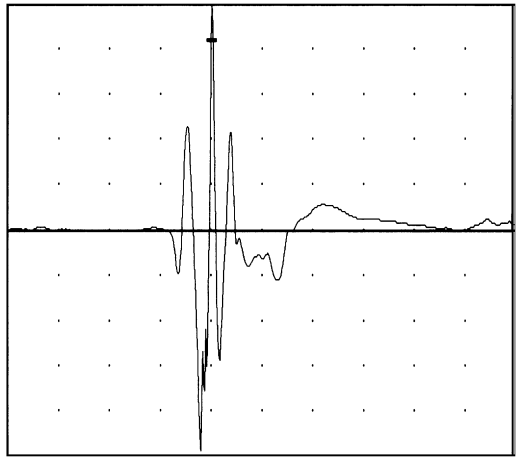

Fig. 9. Neurogenic MUAP. This waveform was recorded with a concentric needle electrode during voluntary activation of the gastrocnemius muscle in a patient with a distal, symmetric diabetic neuropathy. Sweep speed is 5 msec/division, and sensitivity is 1 mV/division. The high amplitude of 10 mV, significantly prolonged duration of 29 msec, and increased complexity ($>$ 10 turns) reflect substantial collateral reinnervation and are markers of chronic motor axon injury and loss.

abnormal recruitment pattern. Recruitment patterns in denervating disease are marked by more rapid motor unit firing and a reduction in the number and rate at which additional motor units are added during increasingly forceful voluntary contraction. EMG of a carefully selected sample of muscles innervated by key nerves and nerve roots can delineate the degree,

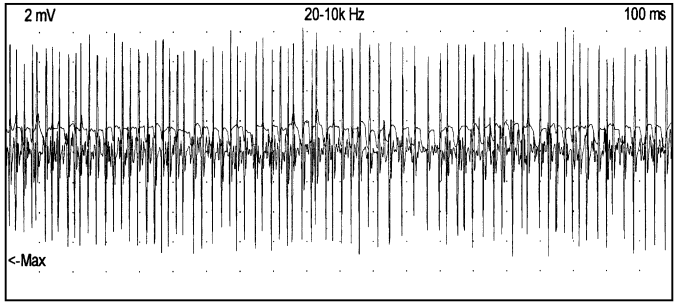

Fig. 10. Reduced interference pattern. This pattern of overlapping MUAP waveforms was recorded during needle EMG from the biceps muscle of a patient with amyotrophic lateral sclerosis during maximal voluntary contraction. The sweep speed is slow at 100 msec/division, and the sensitivity is 2 mV/division. Note the substantial gaps or "picket fence" appearance (in contrast to the normal dense band of overlapping units) caused by the loss of a significant number of motor axons. Note that the MUAP amplitude of the most prominent surviving unit is also increased in this sample (8–10 mV), consistent with concurrent collateral reinnervation by some of the surviving units.

distribution, age, and location of anterior horn cell or motor axon injury [1,8–10].

EMG and nerve conduction studies in the diagnosis of neuropathy

Axonal neuropathy

Axonal injury produces a typical pattern of abnormality on nerve conduction studies. In most instances, axonal neuropathy is a chronic process, but changes may appear on nerve conduction study as early as 3 to 5 days after the onset of acute axonopathy caused by the rapid pace of Wallerian degeneration. In the prototypic distal, symmetric sensory, or sensorimotor neuropathy (the most common types by far), there is initial loss of sensory nerve amplitude in a length-dependent fashion (ie, first in the distal lower extremities) followed by loss of motor amplitudes (in sensorimotor axonopathy), with gradual spread of these abnormalities to the shorter nerve segments in the upper extremities. This is largely because the more distal nerve segments in the legs are farther from their cell bodies (the anterior horn cells and dorsal root ganglia, in and near the spinal cord), which makes maintenance of the axon more difficult, increases its vulnerability to injury, and reduces its capacity to recover. Because myelination is relatively preserved in primary axonal injury, distal latencies, conduction velocities, and late responses are not affected. Late in the course of severe axonal disorders (usually when amplitude has markedly decreased), these parameters may become mildly abnormal because of secondary demyelination or loss of the fastest conducting fibers. Pure sensory axonopathies or dorsal root ganglionopathies affect only sensory nerve amplitudes, leaving the motor responses normal, whereas pure motor axonopathies or anterior horn cell disorders affect only motor responses. Pure motor axonopathies must be differentiated carefully from other processes causing loss of amplitudes on motor nerve conduction studies with normal sensory responses, particularly radiculopathies, anterior horn cell diseases, and distal myopathies.

EMG can provide additional information when motor involvement is suspected in a patient with neuropathy. In a distal symmetric neuropathy, changes appear first in the distal muscles and may move proximally as the neuropathy worsens and the deficits ascend. In severe, acute processes, decreased motor unit recruitment and loss of a full interference pattern on voluntary contraction are the earliest indication of axon loss. With ongoing severe denervation, increased insertional activity and spontaneous activity appear, starting approximately 3 weeks after an acute injury, and may persist as long as the disease process remains active. Neurogenic MUAPs do not appear for at least 2 to 3 months because of the time required for collateral reinnervation to become established. Using these EMG abnormalities, it is possible to estimate the time since the onset of axonal injury and its severity. The degree of axonal loss is particularly important in patients

with treatable neuropathies, because an estimate of axonal integrity enables an estimate of the potential for recovery of strength. Preservation of at least a moderate degree of axonal continuity (as indicated by a mild to moderate, rather than severe, reduction in the interference pattern on full voluntary contraction during EMG) suggests a good chance for further functional recovery, because these surviving axons provide the foundation for collateral reinnervation. If the underlying disease can be controlled, collateral reinnervation is often an effective compensatory process, bringing denervated muscle fibers back into service and restoring strength. When denervating injury occurs slowly enough for collateral reinnervation to become established, nearly normal strength may be maintained even when up to half of the motor axons in a nerve have been lost [1,4,11–13].

Demyelinating neuropathy

Demyelinating neuropathy characteristically causes slowing of nerve conduction as myelin is disrupted and saltatory conduction fails, which causes prolongation of latencies, slowed nerve conduction velocities, temporal dispersion of waveforms, and prolonged or absent late responses. In contrast to axonal neuropathies, motor and sensory amplitudes are relatively preserved. Hereditary demyelinating neuropathies usually produce diffuse and symmetric abnormalities on nerve conduction studies. Most acquired demyelinating neuropathies are at least partially multifocal, however, and produce asymmetric slowing and—classically—multiple areas of conduction block caused by multifocal points of demyelination. Low amplitude waveforms also may be the result of conduction block, but this development usually can be distinguished from axonal injury by comparing the amplitudes of waveforms recorded from different segments of the same nerve. With conduction block, amplitudes from a nerve segment not affected by the block are normal, whereas amplitudes obtained from a segment containing the block are low. Rarely, a distal conduction block (eg, at the wrist) may mimic axonal injury during routine nerve conduction studies. In advanced disease with severe demyelination, secondary axonal degeneration ensues and global declines in amplitude appear.

Needle EMG abnormalities are more limited in purely demyelinating neuropathies. Most of the classic features of denervation on EMG examination are the result of axonal injury producing discontinuity of the axonal connections with the muscle fibers, which is necessary to generate abnormal insertional and spontaneous activity and trigger collateral reinnervation and motor unit remodeling. Because pure demyelination leaves the axons and their connections with the muscle fibers intact, the only abnormalities seen on EMG are changes in motor unit recruitment and loss of a complete interference pattern on full voluntary contraction. These changes occur because although the axons are physically intact, demyelination is severe enough in many of the axons to block their action potentials, functionally

disabling them and preventing activation of their muscle fibers. With severe or longstanding demyelination, secondary axonal changes appear and produce the denervation changes expected with axonal neuropathy. In treatable demyelinating neuropathies, the prognosis for recovery is greatly influenced by the degree of axonal injury. Because the interference pattern may be affected by demyelination itself, axonal injury is best estimated in demyelinating processes by the degree of spontaneous activity or the number of neurogenic MUAPs observed [1,4,5,11–13].

General approach

The approach to any electrodiagnostic study begins with review of the referring information and a directed history and neurologic examination, after which a basic differential diagnosis can be established that will guide planning of the study. Although technical skill and experience are clearly important, a thorough knowledge of neuromuscular disorders and physiology is absolutely essential to the proper planning and interpretation of nerve conduction and EMG studies. Without the clinical guidance provided by a comprehensive knowledge of neuromuscular medicine, the electrical studies needed for delineation of the problem cannot be logically selected, and the generated data are irrelevant and liable to misinterpretation, despite any technical skill on the part of the examiner.

In a patient with suspected neuropathy, nerve conduction studies and EMG should define the type of nerve injury (axonal, demyelinating, or mixed), its distribution (symmetric, asymmetric, multifocal, distal, proximal, or diffuse), and severity and the degree of motor or sensory involvement. Importantly, the study also should be designed to search for other neuromuscular problems that might contribute to or account for the patient's symptoms. Common problems, such as carpal tunnel syndrome, ulnar mononeuropathy at the elbow, and lumbosacral radiculopathy, occur even more commonly in patients with neuropathy (perhaps because of the increased susceptibility of the injured nerve to additional damage from compression and other processes), but the symptoms they cause may be casually attributed to polyneuropathy by many physicians. Such potentially treatable processes may be the major source of a patient's new complaint, even if a neuropathy is also present, and these possibilities must be considered and evaluated carefully.

Nerve conduction studies for neuropathy screening typically include testing of the peroneal and tibial motor nerves and the sural (sensory) nerve in one leg and the median and ulnar motor and sensory nerves in one arm. If focal mononeuropathies are suspected (eg, peroneal mononeuropathy at the fibular head, median mononeuropathy at the wrist, ulnar mononeuropathy at the elbow) and not confirmed by routine studies, special studies may be indicated to definitively search for these focal compressive lesions. In some instances, bilateral studies are needed for side-to-side comparisons.

In patients over the age of 60, the sural and other sensory responses in the distal leg may be lost as a consequence of normal aging and may cloud a search for a mild, pure sensory distal neuropathy. Beyond this basic protocol, the next steps in any nerve conduction study depend highly on the results of these first assessments. Although this standard screen may be sufficient to make the diagnosis in many patients, others require expanded studies, with a broad range of possibilities. Uncommonly, neuromuscular junction dysfunction may be in the differential, and repetitive nerve stimulation may be indicated. Bulbar symptoms (also uncommon) may require evaluation with cranial nerve studies, such as blink reflex testing and facial nerve conduction studies [1,4,5,11–19].

Needle EMG is an important component of the diagnostic assessment of suspected neuropathy. It provides important information regarding the degree and time course of axonal injury in polyneuropathy. It also enables assessment of the proximal motor nerve segments and roots (which are not readily accessible to direct nerve conduction study), thereby providing a means of testing for plexopathy and radiculopathy. EMG also enables assessment of possible primary muscle disease, which can mimic some neuropathies or occur with them. The extent of EMG testing depends on a patient's clinical presentation and the results of the nerve conduction studies. In a clear, distal symmetric neuropathy with symptoms restricted to the lower extremities, needle EMG of one leg and lumbosacral paraspinal muscles may be adequate, but two or even three limb studies may be indicated in other cases [1,4,5,8–10].

Common sources of error during nerve conduction studies

The proper performance and interpretation of nerve conduction studies requires a thorough knowledge of the common pitfalls associated with these techniques. In many individual patients, an electrical diagnosis of peripheral neuropathy is based on a small number of abnormal values. Consequently, careful consideration of technical and physiologic factors is essential to ensure that the abnormalities found are valid and not influenced by technical error. Although some errors are discernable during a review of data after the study is concluded, many errors must be identified and corrected during the examination itself, making the presence of a trained examiner and on-site physician review essential. Faulty data may result either in the misdiagnosis of illness in a healthy patient or an erroneous or missed diagnosis in a patient with neuromuscular disease. These errors are most critical when they influence treatment decisions, prompting either the institution of potentially hazardous therapy in a normal patient or the withholding of needed therapy in a patient with disease. Erroneous electrodiagnostic conclusions may prompt costly, extensive, and sometimes invasive unwarranted diagnostic testing.

Temperature

Temperature is one of the most critical physiologic factor affecting electrodiagnostic studies. Ion channel function, acetylcholinesterase activity, and muscle contractility are a few of the temperature-dependent factors that affect nerve and muscle function [20]. Cooling of nerve profoundly affects the speed of nerve conduction, and velocity linearly increases as limb temperature rises from 29°C to 38°C (Fig. 11). Erroneously increased distal latencies and slowed conduction velocities caused by cold limbs hamper the diagnosis of peripheral neuropathy and obscure the differences between axonal and demyelinating injury; cold temperatures also reduce or mask conduction block [21]. Conventionally accepted limb temperatures range from 34°C to 36°C in the arm and from 31°C to 34°C in the leg; most published normative series use similar ranges. Despite these clear and significant effects, temperature measurement is frequently neglected during nerve conduction studies.

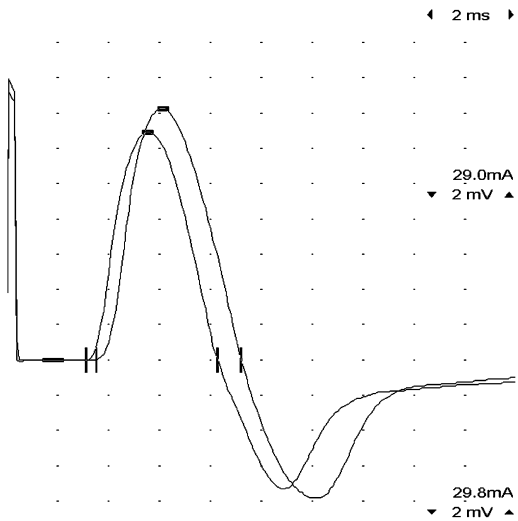

Fig. 11. Temperature effect on distal latency. These two superimposed CMAPs were recorded after stimulation of the median nerve at the wrist, with recording over the thenar eminence at exactly the same sites in a normal subject. The sweep speed is 2 msec/division, and the sensitivity is 2 mV/division. The latency change is caused by the different temperature during each recording. The later waveform (with a latency of 3.5 msec) was recorded from a normal subject at a temperature of 34.7°C, whereas the earlier waveform (with a latency of 3.1 msec) was recorded after heating of the limb with a moist hot pack for 15 minutes, which yielded a temperature of 39.0°C. This 0.4-msec change over approximately 4° is typical and emphasizes the importance of temperature control during nerve conduction studies. The slight decrease in CMAP amplitude also is the result of increased temperature but is not typically dramatic enough to impact final diagnosis.

Most contemporary EMG machines have integrated temperature probes, but reasonably accurate handheld digital devices are readily available. Surface probes measure skin but not nerve temperature, and temperatures near the nerve are generally 1° to 2°C warmer than the overlying skin in cool environments (the reverse in warm environments) [22]. Warm ambient temperature in an appropriate range helps to maintain limb temperature, whereas an excessively cool room makes adequate limb warming challenging. Warming methods include warm water immersion, thermistor-controlled infrared lamp heat, moist heat packs, hot air, and ultrasound, although no method affects each patient or limb uniformly. Warming the limb affects superficial layers more quickly than deeper layers, so brief warming may raise the skin temperature (and the reading reported by a temperature probe on the skin surface) but still not warm the more deeply situated nerve sufficiently to normalize nerve function [23]. Some researchers advocate 30 minutes of warming, but 10 to 15 minutes is more practical and probably sufficient [20,24,25]. Care must be taken not to burn patients who have heat insensitivity caused by sensory loss during heating.

Cooling increases distal latency by 0.1 to 0.3 milliseconds/°C, increases waveform duration, and decreases the severity of spontaneous activity; sensory amplitudes modestly increased in most series. Warming has the opposite effects, and it enhances the detection of conduction block and enhances the degree of decrement recorded during repetitive nerve stimulation. Some studies have calculated temperature correction factors for conduction velocity when limb temperature is abnormally cool (1.5–2.4 m/sec/°C), and some EMG/nerve conduction study devices have a fixed temperature correction option (based on one formula) that recalculates conduction velocity based on temperature probe measurements [20]. These values may be less accurate in diseased nerves, however, especially if demyelination is present, and most researchers agree that limb warming provides more accurate data than formulaic extrapolation.

Age, height, and sex

Nerve conduction velocity rapidly increases during infancy and early childhood, reaching approximately 50% of adult values at full term, 75% at 6 to 12 months of age, and 100% of adult values by 3 to 4 years. Velocity then decreases in adulthood, starting in the second and third decades, possibly because of gradual and progressive loss of the fastest conducting motor axons [26]. The rate and age at onset of this decline are debated and vary considerably between series, but the degree of slowing is relatively minor. Sensory and motor amplitudes decrease more notably with age, although few normative series include significant numbers of elderly control subjects. This effect is most evident in the distal sensory nerves of the legs, which may be unresponsive to stimulation during nerve conduction studies in normal elderly subjects. Rivner and colleagues [27] found that 11 of 46 (24%)

control subjects between the ages of 70 and 79 years and 2 of 5 subjects over the age 80 had absent sural sensory responses. Only 9 of 194 (4.6%) of sural responses in patients aged 60 to 69 were absent, however.

Height is an underappreciated factor that inversely correlates with sensory and motor nerve conduction velocity [27]. The degree of change varies considerably from subject to subject, but increased height may reduce conduction velocity more than advanced age. Velocity decreases approximately 2 to 3 m/sec for each 10 cm of height above average; amplitude is influenced much less. This slight slowing of conduction velocity in tall subjects becomes an issue when their studies are compared with normative ranges, which are based on subjects of average height. Women have slightly faster mean conduction velocity than men, but this group discrepancy does not persist after correction for height differences between the sexes [27,28].

Stimulation

Submaximal stimulation

Nerve conduction studies presume that supramaximal stimulation is delivered, which results in depolarization of all axons within the tested nerve. When stimulation of all the axons within the tested nerve is not achieved, inadequate (submaximal) stimulation occurs and artifactually low amplitude waveforms are generated during motor and sensory nerve conduction studies (Fig. 12). These artifactually low amplitudes can mimic axonal injury and partial conduction block. Conduction velocity may slow slightly if the largest—and fastest—conducting axons are not activated because conduction velocity calculations are based on the latencies of these fastest conducting fibers. Stimulating at four times the minimal threshold level needed to evoke a consistent initial response is one technique used to estimate the approximate level needed for supramaximal stimulation [29]. One common mistake is to stop progressively increasing the stimulus intensity as soon as the response amplitude crosses into the normal range, when it may be normal but still submaximal. This error especially complicates interpretation of longitudinal studies and side-to-side comparisons.

Most submaximal stimulation results from improper stimulating electrode placement (away from the intended nerve) or failure to use adequate stimulus intensity, but other factors also may play a role. Perspiration, dirt, or excess electrode paste can shunt current away from the nerve; dead skin is also a stimulation barrier. Cleaning and gently abrading the stimulus sites can minimize these factors and reduce artifact. Obesity also impedes surface nerve stimulation, most prominently sensory nerve amplitudes, which are reduced on average 20% to 25% between the highest and lowest thirds of body mass index [30]. Diseased motor axons may have reduced excitability and require high intensity and long duration stimulation (1.0 msec), especially when demyelination is present.

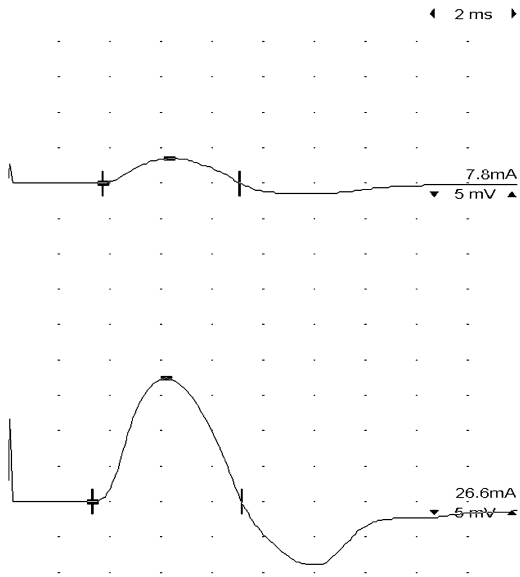

Fig. 12. Submaximal stimulation. These two CMAPs were recorded after stimulation of the median nerve at the wrist, with recording over the thenar eminence at exactly the same sites. The sweep speed is 2 msec/division, and the sensitivity is 5 mV/division for both waveforms. The stimulus intensities are also labeled to the right of each potential. The top waveform was recorded using low intensity stimulation (7.8 mA), which resulted in incomplete, submaximal stimulation of the nerve and an artifactually low CMAP amplitude of 3.5 mV. The bottom waveform was recorded with supramaximal stimulation (26.6 mA), which produced complete depolarization of all motor axons in the tested nerve and a dramatically larger amplitude of 17.5 mV. Further increases in stimulus intensity resulted in no further increases in amplitude.

At some sites, it may be challenging to fully stimulate the nerve with surface electrodes, even with maximal stimulus intensity and duration, usually because the nerves are deeply situated (eg, the brachial plexus at Erb's point, the popliteal fossa, the ulnar nerve at the cubital tunnel). Proximal conduction block across the brachial plexus can be difficult to assess in some patients because of this problem.

Excessive stimulation and stimulus spread

Exceeding supramaximal stimulus intensity does not increase waveform amplitude further but can generate erroneous data by depolarizing a larger field than desired. Such excessive stimulation increases the distance the stimulus travels from under the cathode, which results in nerve depolarization beyond the actual position of the stimulating electrode (creating a virtual cathode). As a result, the nerve segment length tested is effectively shortened and, consequently, the measured latency and calculated conduction velocity are erroneously reduced [24]. When the stimulating electrode poles (anode

and cathode) are reversed, the improperly placed (more distal) anode hyperpolarizes the underlying nerve, forcing the propagating depolarization wave to pass through this hyperpolarized region and reducing stimulus effectiveness (anodal block). More critical, however, is the mistaken distance measurement point if the reversal is not identified, which adversely affects conduction velocity and distal latency.

A stimulus also can spread to an adjacent nerve when nerves are in close proximity, such as at the brachial plexus, wrist, and popliteal fossa, especially when high stimulus intensities are required. Optimal positioning of the stimulating electrodes and visualization of the muscles activated can help to confirm that the selected nerve is primarily stimulated. A change in amplitude, an initial positive deflection, or altered waveform morphology between stimulation sites alerts the examiner to this problem.

Under certain circumstances, stimulus spread can mimic conduction block when simultaneous activation of two closely situated nerves at a distal stimulation site results in artifactually high distal amplitude and a lower, but valid, amplitude results from proximal simulation where the nerves are not in close proximity. This scenario can be mistaken for focal conduction block between the proximal and distal sites. Near nerve stimulation methods can eliminate spread by delivering a supramaximal stimulus at a much lower intensity, but these techniques are more invasive and less commonly performed [29].

Recording techniques and issues

Antidromic versus orthodromic sensory recordings

Many sensory nerves can be studied using either orthodromic stimulation (distal stimulation with proximal recording, in the physiologic direction of flow for normal sensory impulses) or antidromic methods (proximal stimulation with distal recording, opposite to the physiologic direction of impulse flow). All motor studies are orthodromic (stimulation of the nerve proximally, with recording from a distal innervated muscle). Knowing which technique was used for sensory recordings is essential for valid data interpretation. Latency and velocity measures are equivalent with either method, but antidromic studies generate larger sensory amplitudes, primarily because the nerves are more superficial at distal recording sites [31]. Antidromic stimulation often activates both the motor and sensory axons in a mixed nerve, which results in concurrent muscle activation. The inadvertently triggered CMAP, which is usually much larger than the sensory response, can obscure part of the desired sensory potential and measurements of latency and amplitude can be compromised [24]. Occasionally, the motor response can obscure the sensory response entirely; however, a delayed and long duration waveform should alert the examiner to this artifact.

Distance between recording electrodes and nerve

Improper or inconsistent recording electrode placement is a common error during nerve conduction studies. Conventional electrode placement for motor nerve conduction studies involves positioning the active (G_1) electrode over the muscle belly at the motor point (the surface point closest to the neuromuscular junction) and the reference electrode (G_2) at an electrically inactive point on the muscle tendon, approximately 3 to 4 cm more distal. After motor nerve stimulation, this montage produces a diphasic waveform with a large initial negative (upward) deflection. An initial positive (downward) deflection preceding the larger negative deflection indicates incorrect G_1 electrode positioning away from the motor point or a volume conducted potential from another muscle (stimulus spread) (Fig. 13). An

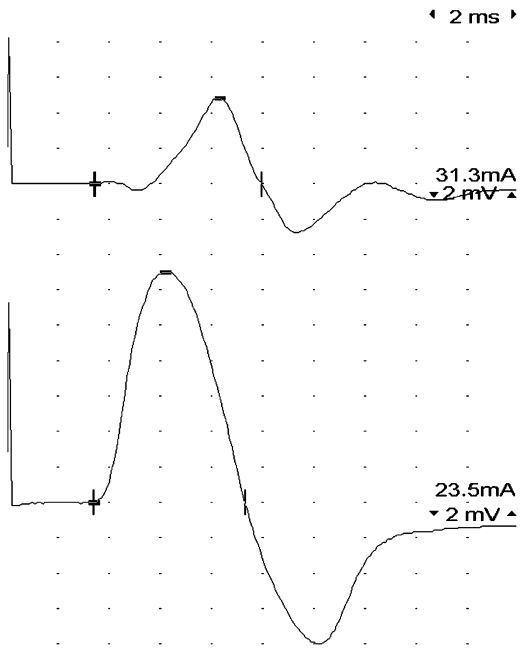

Fig. 13. Effect of recording electrode position on the CMAP. These two CMAPs were recorded after stimulation of the median nerve at the wrist. The top waveform was recorded with the active recording electrode 10 to 20 mm off the motor point of the muscle, whereas the bottom waveform was recorded with the active electrode directly over the motor point. Note the initial positive (downward) deflection immediately preceding the major negative (upward) deflection in the top waveform. This small initial positive deflection clearly indicates origination of the depolarization wave in the muscle at a distant site (the motor endplate) from the misplaced recording electrode. CMAP negative peak amplitude is also substantially reduced and latency marker placement is problematic because of the leading positive phase. Careful attention to active recording electrode placement is critical, because slight misplacement off the motor point can affect CMAP waveform parameters significantly.

inverted potential—an initial large positive wave and smaller later negative wave—occurs when the active and reference recording electrodes are reversed. For sensory studies, the recording electrode must be placed as close to the nerve as possible because sensory nerve action potential amplitude rapidly declines with increasing distance between the nerve and the recording electrode. Consequently, even gently pressing the surface electrode toward the nerve increases the SNAP amplitude by 10% to 20% [32]. Larger finger size also increases the distance between the nerve and the recording electrode. For these and other reasons, such as skin and tissue impedance, near-nerve recordings (recordings made with a needle electrode placed through the skin and next to the nerve) are typically three to seven times larger than surface recordings [24,31].

Distance between active and reference electrodes

Motor and sensory waveforms are affected by this distance, especially amplitude and waveform duration (because of differing degrees of phase cancellation and summation of the axon potentials comprising the larger SNAP waveforms) [24,33,34]. With normal human nerve conduction velocities, the optimal distance between these electrodes for proper capture of the full rising and falling phases of waveforms (recording from the nerve) is 3 to 4 cm. Most fixed bar electrodes use this distance.

Recording electrode size

Little attention is generally paid to the recording electrodes. Studies suggest that response amplitude declines slightly with larger electrodes [31,32]. Sensory amplitudes fall 10% to 15% with a 20-mm and 20% to 25% with a 40-mm recording electrode when compared with a 5-mm electrode [32]. Many modern disposable electrodes are significantly larger than the reusable electrodes used to generate most of the widely used normative data. This discrepancy is potentially relevant when amplitudes are borderline, but the issue is probably not a source of significant error and is not sufficient to discourage use of convenient, although more expensive, self-adhesive electrode sets.

Filter settings, sensitivity, and sweep speed

Most contemporary machines use standard high- and low-frequency filter settings for motor and sensory waveform recording. Changes can be made manually that can adversely affect nerve conduction studies and EMG. Filter settings affect evoked response amplitudes and latencies (eg, increasing the low-frequency [high pass] filter reduces some artifacts but also reduces response amplitudes). Examiners should be aware of the standard filter settings on their equipment and confirm that they correspond with the ranges used to record the normative data used for reference. If changes are made

for any reason, the effects of these changes on the measured waveform values must be considered.

Most current machines use an internal algorithm to mark waveforms at standard sensitivity and sweep speed setting. Computerized marker placement is often incorrect, however, and each cursor must be reviewed and may require manual adjustment. Care must be taken to mark all latencies and amplitudes at a consistent sensitivity setting, because magnifying the waveform by increasing the sensitivity alters the apparent position of the latency cursors, changing latency, and conduction velocity (Fig. 14). It is tempting to record the waveform at a low sensitivity and then enlarge the waveform later by increasing the sensitivity setting to readjust the markers. The higher the sensitivity setting, the shorter the latency of a waveform appears; a gain setting of 1 mV/division is most commonly used for motor studies. Altering sweep speed causes a similar error and should be consistent

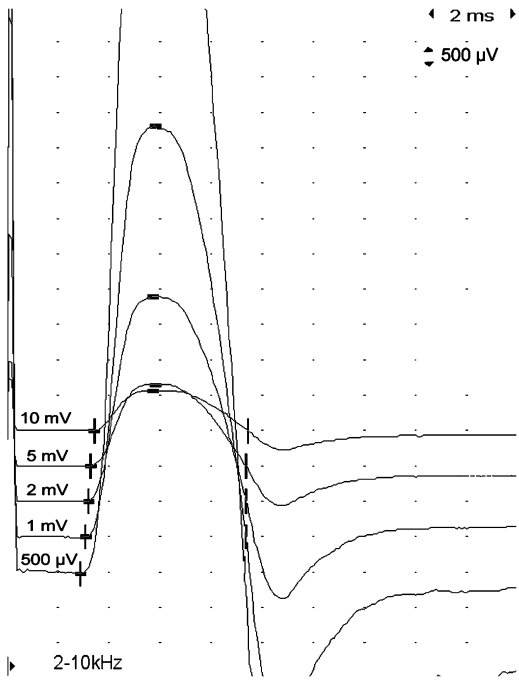

Fig. 14. Effect of sensitivity settings on measured latency. These five CMAPs were recorded after stimulation of the median nerve at the wrist, with recording over the thenar eminence at exactly the same sites. The sensitivity settings for recording of each waveform were increased from top to bottom, however (10 mV/division, then 5 mV, then 2 mV, then 1 mV, then 500 µV or 0.5 mV/division). As the sensitivity of the display is increased, the onset of the initial negative deflection becomes better defined and appears earlier, producing earlier and earlier onset latencies (3.4 msec at 10 mV, 3.3 at 5 mV, 3.2 at 2 mV, 3.1 at 1 mV, and 2.9 msec at 500 microvolts). This illustrates the importance of measuring latency at standardized and consistent sensitivities (usually 1 mV/division for motor studies) to facilitate reliable comparisons with normative data.

from study to study. A highly amplified display also can reveal a faster antidromic sensory response, not evident at conventional gain settings, that may complicate waveform marking. In instances of severe amplitude loss, higher than usual sensitivity settings may be required to measure small waveforms. In these cases a sensitivity setting as close to standard as the waveform size will allow is advised.

Effect of stimulus artifact

Excessive stimulus artifact is a common problem, especially with sensory studies. If the initial baseline is shifted and no isoelectric period occurs between the stimulus and evoked waveform, the waveform shape, measured amplitude, and onset latency are compromised; falsely increased and decreased latency and amplitude measures can result. Sensory amplitude is vital in the evaluation of peripheral neuropathy. Attention to skin preparation, appropriate and not excessive electrode gel, induced current between stimulating and recording wires, and effective grounding are primary concerns, and numerous other measures are recommended to avoid problems [24]. Shielded recording cables are used in some laboratories, and early signal digitization is accomplished by some machines to help minimize this problem.

Waveform marker placement

Conventional rules for marking nerve conduction studies waveforms differ between motor and sensory studies. The distal motor latency is marked at the onset of the initial deflection, whether positive or negative. The waveform duration is measured from its onset to the negative wave return to baseline (automated area calculations also depend on the waveform duration markers). Motor amplitudes are marked from the baseline to the primary negative waveform peak. Sensory latency is marked either at the initial positive peak of the waveform (onset latency) or the later larger negative peak (peak latency); normative latency data are published for both methods, and each laboratory typically uses one or the other for sensory latency measures. Only onset latency should be used to calculate sensory nerve conduction velocity, however. Sensory waveform duration is also measured from its onset to baseline return. Sensory amplitudes are typically measured either from the initial or terminal positive peak to the largest negative peak; the initial baseline is used if there is no initial positive peak.

Errors in marker placement, either by computer algorithm or manual settings, can alter latency (and resultant conduction velocity calculations) and duration and amplitudes, generating artifactual data, which can mimic demyelinating or axonal injury or both. Consequently, careful review of marker placement, whether automated or manual, is an essential step. If normative data from other laboratories are used for reference (rather than a locally generated normative data set), the same rules for marker placement used to acquire that normative data must be followed during testing of new patients.

Distance measurement between stimulating and recording sites

Distance measurement between stimulating and recording sites is often assumed to be simple, but measurement errors are common. Distance should be measured from the stimulating cathode center to the active recording electrode center. Slight skin movement and misreading or misplacing the measuring tape are leading causes of error. Erroneously short distances artifactually increase conduction velocity and reduce latencies, masking true abnormalities; erroneously long distances reduce velocity and increase latencies, mimicking demyelinating injury. For a 10-cm segment, a 1-cm measurement error creates approximately a 10% error in conduction velocity. This error is amplified with shorter distances and in nonlinear segments, for example, when a nerve curves around a joint. Most surface measures are slightly shorter than actual nerve length, but this difference is usually negligible unless the course is not linear [24]. Limb position is critical in some circumstances. For example, in studies of the ulnar nerve across the elbow, the nerve folds when the arm is extended and is roughly straight (but not stretched) when the elbow is slightly flexed at 70°, making standardized elbow positioning (usually 70°–130°) critical for distance measures in this segment [35,36]. A falsely slow conduction velocity across the elbow and a potential false diagnosis of ulnar mononeuropathy may result if the elbow is too straight [36]. Most nerves are measured linearly by their estimated course, regardless of whether the nerve is anatomically straight. When the course of a nerve is not linear and not affected by joint position (eg, across the spiral groove, shoulder, or pelvis), obstetric calipers provide a more accurate distance measurement.

Fixed distances are used by many laboratories for sensory studies and distal motor segments to improve consistency of latency measurements and ensure accuracy when latencies and velocities are compared with normative data. Although amplitude is typically affected less by changes in distance from study to study, sensory amplitude progressively declines with increasing distance between the stimulation and recording sites because of physiologic temporal dispersion, making standardized distances important for sensory amplitude measures as well.

Anatomic variants

Variations in peripheral nerve anatomy are prevalent but usually do not lead to misdiagnosis during routine nerve conduction studies. Two common variations can lead to errors when pronounced: the median-to-ulnar nerve anastomosis (Martin-Gruber anastomosis) and the accessory deep peroneal nerve.

The Martin-Gruber anastomosis is a bundle of ulnar nerve fibers that travel proximally with the median nerve, then cross to the ulnar nerve in the

forearm and continue on to innervate selected ulnar small hand muscles. Three subtypes are described depending on the innervated muscular targets. This anastomosis occurs in 15% to 31% of the general population and is often bilateral, but the percentage of fibers involved is usually small and clinically insignificant. When enough fibers are involved, however, nerve conduction studies may be affected. The primary diagnostic clue is a difference between median or ulnar amplitude between elbow and wrist stimulation not caused by stimulating or recording errors. This difference appears as either an increase in CMAP amplitude with stimulation of the median nerve at the elbow compared with stimulation of the median nerve at the wrist or a decrease in amplitude with stimulation of the ulnar nerve at the elbow compared with stimulation of the ulnar nerve at the wrist. Normally, there is minimal change in CMAP amplitude between these sites. The anastomosis is demonstrated by performing routine median and ulnar motor studies, followed by stimulation of both nerves while recording from a single hand muscle. Ulnar mononeuropathy and conduction block are possible misdiagnoses resulting from a failure to recognize a Martin-Gruber anastomosis. A small anastomosis is frequently revealed by a superimposed median neuropathy at the wrist, which unveils the faster anomalous ulnar fibers that travel with the median nerve at the elbow but not through the carpal tunnel [37].

The accessory deep peroneal nerve is present in approximately 20% of subjects and can lead to the mistaken conclusion that reduced peroneal motor amplitude is caused by underlying peripheral neuropathy. In this variant, some axons from the superficial peroneal nerve, which normally involute during embryogenesis, instead persist to innervate a portion of the extensor digitorum brevis muscle, which is ordinarily solely innervated by the deep peroneal nerve. The extensor digitorum brevis serves as the primary recording site for routine peroneal motor nerve conduction studies. The clue to this anomaly is the presence of a smaller evoked CMAP amplitude with routine deep peroneal nerve stimulation at the ankle site (while recording over the extensor digitorum brevis) than with peroneal nerve stimulation at the knee. Because the anomalous peroneal branch is distant from the standard deep peroneal stimulation site at the ankle, the motor axons it carries are not activated with standard stimulation at the ankle and a portion of the extensor digitorum brevis remains unstimulated, generating a smaller CMAP (in contrast to stimulation at the knee, which activates the common peroneal nerve trunk above the branch point, activating all fibers and generating the full extensor digitorum brevis CMAP). If care is not taken to deliver supramaximal stimulation at the knee, artifactually low amplitudes may be seen with stimulation in both locations for different reasons, which reinforces a misdiagnosis of axonal loss. The anomalous branch is identified by stimulating behind the lateral malleolus while recording from the extensor digitorum brevis. In a subject with standard anatomy this site should contain no peroneal nerve fibers. If a response is obtained from this normally quiescent site, the presence of the branch is confirmed [38].

Late responses

F waves are low amplitude late responses best triggered by supramaximal stimulation. Waveforms potentially confused with F waves include axon reflexes, A waves, and surface recording of incompletely relaxed muscle [39–41]. Axon reflexes are uncommon, highly persistent, intermediate latency potentials triggered by submaximal stimulation, thought to be caused by ephaptic transmission of impulses between adjacent motor axons within a damaged nerve. Unlike F waves, axon reflexes are relatively fixed in shape and latency and usually occur in the setting of reinnervation. They are usually abolished by higher stimulation intensities, similar to H reflexes [39]. In contrast, A waves are common but incompletely understood phenomena found during routine F wave studies; they share some features with true F waves, but latencies are usually shorter and shape and latencies are much more constant. A waves are more prevalent in neurogenic disorders [39]. Excessive surface recorded volitional muscle activity, easily identified using the machine loudspeaker during F wave recording, also can hamper F wave identification.

The most commonly used F wave measure is minimal onset latency. An inadequate number of stimulations can affect results. Studies show that 10 stimulations produce values within 95% of true values (within 1 msec) for minimal and mean latencies (based on 100 stimulations) [40,41]. Care must be taken not to overinterpret values near the upper limit when fewer than 10 to 20 stimulations are delivered. Because minimal latency is based on the single shortest waveform, one normal axon may yield a normal overall minimal latency in an otherwise abnormal nerve. Consequently, a normal F wave study does not exclude disease. F wave persistence, the percentage of stimulations that produce a response, is 90% with 10 stimuli and 97% with 20. Persistence can be increased by slight muscular contraction, however. Peroneal nerves have lower F wave persistence than other nerves typically studied, which limits their sensitivity. Less common measures, such as amplitude comparisons and minimal to maximal latency (chronodispersion), require considerably more stimulations to produce a reliable number [41].

H reflexes from the soleus muscle stimulating the tibial nerve are sensitive indicators of large fiber polyneuropathy or S_1 root disease that correlate highly with the Achilles deep tendon reflex. Long duration, submaximal stimuli are optimal; normal responses are suppressed by excessive stimulus intensity. Also at higher intensities, possibly confounding F waves are recordable. Responses are bilaterally absent in a percentage of normal controls, more commonly in older subjects. The reflex is enhanced with activation maneuvers similar to deep tendon reflexes; latencies are affected by similar factors, such as temperature, age, nerve length, and conduction velocity. It highly correlates with the presence or absence of the deep tendon reflex on physical examination [39].

Summary

Electrodiagnostic studies are a critical tool for the identification and study of peripheral neuropathy, enabling definition of the pathophysiologic type of nerve injury, its distribution, severity, and the degree of motor or sensory nerve involvement. These data help to differentiate the varieties of neuropathy from other neuromuscular diseases. Nerve conduction studies and EMG, although widely performed, are complex techniques and are subject to a wide range of artifacts, which can result in missed or erroneous diagnoses. Important factors to consider, in addition to proper technique, include regulation of limb temperature, patient age and height, regulation of stimulus strength, recording electrode design and placement, filter settings, sensitivity and sweep speed settings, the effects of stimulus artifact, waveform marker placement, proper measurement of distance between stimulating and recording sites, and the variants of peripheral nervous system anatomy. Without proper education, training, and experience in neuromuscular disease and the techniques of electrodiagnosis and careful attention to potential sources of error, the critical information needed to properly diagnose and treat patients with neuropathy is unreliable and may lead to wasted resources and patient injury.

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