CHAPTER 56B

Nerve Conduction Studies

Mark A. Ross

Nerve conduction studies involve recording, measuring, and interpreting the responses of individual peripheral nerves to electrical stimulation. These tests expediently provide extensive information regarding the state and function of the peripheral nerves. They permit independent assessment of sensory and motor fibers and allow objective and quantitative measurements of nerve function that are not obtainable with physical examination. Nerve conduction studies may delineate the extent of a diffuse disorder of peripheral nerves or localize a focal nerve lesion. They may reveal evidence of axonal degeneration or demyelination of peripheral nerves and gauge the severity of the process. For certain nerves, F wave, H reflex, and blink reflex studies permit assessment of the most proximal nerve segments. Repetitive nerve stimulation studies of motor nerves allow evaluation of neuromuscular transmission.

When nerve conduction studies are completed, the results are integrated with clinical information and electromyography (EMG) findings to generate a conclusion regarding peripheral nerve function. This integration of information is essential, because technical factors and neuromuscular disorders other than peripheral nerve disease can produce abnormal nerve conduction results. Conventional nerve conduction studies are limited by the nerves amenable to study; they assess only the fastest-conducting nerve fibers, and there are numerous potential sources of error.

PERIPHERAL NERVE ANATOMY

A nerve cell consists of a cell body, or perikaryon, and its elongated cell process, the axon. The location of peripheral nerve cell bodies varies according to the nerve fiber type. The cell bodies of somatic motor nerves are located in the anterior horn of the spinal cord, and those of cranial nerves are within brain stem nuclei. Cell bodies of somatic sensory nerves are the dorsal root ganglia, located within the spinal canal just proximal to the intervertebral foramen. The major cranial sensory nerve, the trigeminal nerve, has cell bodies in the gasserian ganglion.

The peripheral nerve consists of thousands of individual axons arranged into multiple fascicles and supported by several different connective tissues (Fig. 1). The connective tissue surrounding the entire nerve and coursing between individual nerve fascicles is called...
epineurium. It contains collagen, fibroblasts, blood vessels, lymphatics, and fat. Perineurium refers to a specialized layer of cells that surrounds each fascicle (41). These cells are called perineurial cells and are joined by tight junctions. The perineurial cells provide a diffusion barrier from the epineurial extracellular space (52). Endoneurium refers to the connective tissue matrix around individual axons.

Myelinated axons are those fibers wrapped with myelin supplied by Schwann cells (Fig. 1). The Schwann cells are arranged linearly along the course of the axon and are connected by a continuous basal lamina to form a conduit for the axon, known as the Schwann cell tube. Myelin, the proteophospholipid Schwann cell membrane, is wrapped around the axon spirally, forming multiple layers known as myelin lamellae. Myelin completely covers the axon except at the junctions between Schwann cells—called nodes of Ranvier—which are free of myelin. Unmyelinated axons are not spirally wrapped by myelin lamellae. Rather, they are individually encased, with other unmyelinated axons, within a small portion of a Schwann cell membrane (Fig. 1).

PERIPHERAL NERVE PHYSIOLOGY

The resting membrane potential physiology for peripheral nerve is similar to that described for skeletal muscle in Chapter 56A. The nerve action potential (NAP) differs from the muscle fiber action potential (MFAP) in the mechanism and speed with which it propagates along the cell membrane. In myelinated peripheral nerves, virtually all the sodium channels of the axon membrane are located at the nodes of Ranvier (42). Because current traverses the membrane via sodium channels in the nodal regions and myelin prevents passage of current through the internodal nerve segments, action potentials travel along myelinated nerves by jumping from node to node (Fig. 2). This process, known as saltatory conduction (14,47), results in much faster conduction of action potentials along myelinated peripheral nerves than unmyelinated nerves or skeletal

FIG. 1. Cross-sectional diagram of a peripheral nerve, showing three fascicles and the nerve's connective tissue elements. The magnified view on the left shows the relationship of a Schwann cell and its membrane (myelin) to the axon. (With permission from ref. 43.)

FIG. 2. Saltatory conduction along a myelinated fiber. The cathode of an electrical stimulator (open arrow) locally depolarizes the axon membrane, resulting in reversal of the inside-negative resting membrane potential. Local currents produced (broken arrows) jump across myelin segments (shaded areas) to reach adjacent nodes of Ranvier, where the bare axon membrane has a high concentration of sodium channels. The resting membrane potential will subsequently reverse at these nodes, and the action potential will propagate along the nerve in both directions from the stimulus site. (With permission from ref. 24.)
nerve conduction studies

TECHNIQUES AND PRINCIPLES OF NERVE CONDUCTION STUDIES

Equipment and Settings

The equipment needed to perform nerve conduction studies includes an electrical stimulator, a differential amplifier, and a storage oscilloscope. Modern commercial equipment incorporates these components into a single machine. The oscilloscope sweep is not free-running as it is with an EMG. Rather, it is triggered by depressions of either a foot switch or a hand-held stimulator button. The sweep or trace is activated slightly before the stimulus occurs, so that the latency between the stimulus and the recorded response can be measured. The sweep speed is based on the expected latency of the response and varies from 1 to 10 milliseconds per centimeter (insect) for routine studies. The filter band pass may be set from 20 Hz to 2 kHz for sensory studies and from 2 to 10 Hz for motor studies.

Nerve Stimulation

Application of an electrical stimulus of sufficient intensity and duration near a peripheral nerve depolarizes the nerve and generates a NAP. This is routinely accomplished with two surface electrodes placed on the skin directly over the nerve (Fig. 3). A square wave pulse of current is passed between the cathode and anode of the stimulator. The negatively charged cathode depolarizes an area beneath it (Fig. 2). The cathode is positioned closest to the recording electrodes, with

FIG. 3. Median nerve conduction study. The hand-held stimulator depolarizes the median nerve at the wrist, with the cathode (negative pole) positioned distally relative to the anode (positive pole). A sensory nerve action potential (A) is recorded with ring electrodes (active, proximal) around the index finger. A compound muscle action potential (B) is recorded with plate electrodes taped over the muscle belly of the abductor pollicis brevis muscle (active electrode) and its tendon (reference electrode).
the anode located 2 to 3 cm in the opposite direction. To ensure simultaneous activation of the nerve’s large fibers, a supramaximal stimulus is given. A stimulus is considered supramaximal when the current or voltage is 20% greater than that needed to obtain a maximal response (2). A maximal response is recognized when an additional increase in stimulus intensity does not produce a further increase in amplitude or area of the evoked response.

Constant-current stimulators are generally preferable to constant-voltage stimulators, the former regulate the current that reaches the nerve within the limits of the impedance of intervening tissues. The stimulus duration ranges from 0.05 to 1.0 msec. Routinely, the stimulus duration is set at 0.1 msec and the current or voltage is gradually increased to regulate the stimulus intensity. The stimulus duration may also be increased to achieve a supramaximal stimulus. With a surface stimulus of 0.1-msec duration, a healthy nerve can usually be fully activated with 5 to 40 milliamperes (mA) or 100 to 300 volts (V) (25). Activation of a diseased or inordinately deep nerve may require 60 to 75 mA or 400 to 500 V (25). When a nerve is directly stimulated (e.g., during intraoperative monitoring or when a stimulating needle electrode is placed close to a nerve), considerably less current is needed to fully activate the nerve. In these situations, the stimulus duration is decreased to 0.05 msec and the current or voltage is limited to 5 to 8 mA or 25 to 30 V, respectively (7).

The nerves most commonly studied in the electrophysiology laboratory include the facial, median, ulnar, radial, peroneal, tibial, and sural nerves. However, many other nerves can be studied when clinically indicated (8,25,35). To detect evidence of focal abnormalities, a nerve should be stimulated at multiple sites along its course. For example, the median nerve may be stimulated at the palm, wrist, elbow, axilla, and Erb’s point. The responses generated with each of these stimulation sites are recorded and analyzed, and conduction velocity is calculated for each nerve segment.

Recording Nerve Responses

The principles and terminology for recording electrical activity from nerves are the same as those described for skeletal muscle in Chapter 56A. Briefly, the electrical potential difference between two recording electrodes is amplified and displayed on an oscilloscope. By convention, a waveform deflection above the baseline is called negative, and one below the baseline is called positive.

Once initiated, the NAP travels along a nerve and can be recorded at some distant site. For sensory fibers, the NAP is recorded with electrodes placed directly over a sensory nerve branch and is called the sensory nerve action potential (SNAP) (Fig. 3A). In the case of motor nerve fibers, the NAP recording is made indirectly, with muscle acting as intermediary. Via the process of neuromuscular transmission (discussed in a later section), the motor NAP induces de-
polarization of muscle fibers. The summed potential of all the muscle fibers that are depolarized is called the compound muscle action potential (CMAP), or M wave (Fig. 3B).

The terms orthodromic and antidromic are used to describe different recording techniques. Orthodromic indicates that action potentials propagate along nerve fibers in the same direction as occurs physiologically. Antidromic indicates that action potentials propagate in the direction opposite to that which occurs physiologically. Electrical stimulation of a mixed nerve (combined sensory and motor) produces action potential propagation in all fibers and in both directions from the stimulus site (Fig. 4). When a mixed nerve is stimulated, recording a CMAP from a muscle innervated by the nerve is considered orthodromic, and recording a SNAP from one of the nerve's digital branches is considered antidromic.

**Sensory Nerve Action Potential**

When surface recording electrodes are used, antidromic sensory nerve conduction studies are preferred because they permit recording much closer to the nerve and thus yield larger amplitude SNAPs than those obtained with orthodromic recording (Fig. 5). The SNAP usually has a negative waveform of 1 to 2 msec duration, followed by a smaller positivity. The parameters for SNAPs are latency and amplitude at each stimulus site. Latency is measured in milliseconds to the onset of the SNAP negative wave. Latency values increase with more proximal stimulation sites. **Amplitude** is measured in microvolts (μV) from the baseline to the SNAP negative peak. Using the antidromic technique, the SNAP amplitude decreases with more proximal stimulation sites (Fig. 6). This occurs because individual axons normally conduct at slightly different velocities (physiologic temporal dispersion); thus their action potentials arrive at the recording electrodes in a mildly desynchronized manner (23). The degree of desynchronization is increased when the action potentials travel over a greater distance, such as with more proximal stimulation sites. This results in the action potentials of some nerve fibers occurring out of phase with the action potentials of other nerve fibers, producing cancellation of their electrical signals and a reduced ampli-
FIG. 6. Simultaneous recordings of compound muscle action potentials (CMAPs) from the thenar eminence and sensory nerve action potentials (SNAPs) from the index and middle fingers after stimulation of the median nerve at the palm, wrist, elbow, and axilla. Proximal stimulation produced progressively smaller-amplitude SNAPs but little change in the CMAPs. (With permission from ref. 23.)

A. Sensory Nerve Action Potentials

Stimulation

Fiber

F

S

Superimposed Sensory Fiber Potentials

F

S

Summed Sensory Fiber Potentials

F

S

B. Compound Muscle Action Potentials

Stimulation

Motor Fiber

F

S

Superimposed Motor Fiber Potentials

F

S

Summed Motor Fiber Potentials

F

S

FIG. 7. Physiologic temporal dispersion of nerve action potentials and phase cancellation. A: With distal nerve stimulation (open arrows), sensory nerve action potentials (SNAPs) from fast-conducting (F) and slow-conducting (S) fibers arrive at the recording electrode at nearly the same time, creating a larger-amplitude SNAP when summed. With proximal nerve stimulation (closed arrows), the SNAP latencies from S fibers are longer than those from F fibers (physiologic temporal dispersion). SNAPs from S fibers arrive at the recording electrodes out of phase with the SNAPs from F fibers. This results in phase cancellation, giving a lower-amplitude SNAP when summed. B: The same variation in conduction velocities of F and S motor nerve fibers occurs, but because of the relatively long duration of the CMAP, the accentuated latency shifts of individual motor nerve fiber potentials with proximal stimulation do not result in phase cancellation. Hence, the CMAP changes little with proximal stimulation. (Modified with permission from ref. 23.)
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Compound Muscle Action Potential

The CMAP is routinely recorded with surface electrodes. The active electrode is placed over the muscle’s motor point and the reference electrode is placed over the muscle’s tendon (Fig. 3). The parameters assessed include amplitude, measured from baseline to negative peak; onset latency of the negative wave; and duration of the negative wave. The amplitude of CMAPs is normally in the range of 3 to 20 millivolts (mV). The CMAP amplitude remains relatively constant at distal and proximal stimulation sites (Fig. 6). Although proximal stimulation also causes physiologic temporal dispersion in motor fibers, it produces little effect on the CMAP amplitude. The reason for this is that the duration of the CMAP is much longer than that of the SNAP, and the slight latency shifts of individual MFAPs with proximal stimulation produce less phase cancellation (Fig. 7B).

Nerve Conduction Velocity

Calculation of nerve conduction velocity is based on the measured values for response latencies and surface distances between stimulating and recording electrodes. Dividing the distance the NAP travels from the stimulus to the recording electrode by the response latency gives the nerve conduction velocity (Fig. 8). However, for the most distal motor nerve segment, the true nerve conduction velocity cannot be calculated. The reason is that the motor response latency includes not only time for conduction along the nerve but also for spread of the action potential along intramuscular nerve terminals, neuromuscular transmission, and action potential conduction along the more slowly conducting muscle fibers. By stimulating the motor nerve at both proximal and distal sites, one can calculate the nerve conduction velocity for the proximal nerve segment by dividing the distance between these sites by their latency difference. For sensory fibers, the conduction velocity in the most distal nerve segment can be calculated directly by dividing the segment distance by its latency. Nerve conduction velocities vary with age, reaching adult values of approximately 50 to 70

Stimulus (A)    Stimulus (B)    Recording (C)

<p>| | | |</p>
<table>
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</table>

NCV for segment BC
Sensory fibers:

Distance A to B (cm) * 10 = NCV (m/s)
Latency A (ms)

Motor fibers: NCV for segment BC cannot be calculated

NCV for segment AB
Motor or sensory fibers:

Distance A to B (cm) * 10 = NCV (m/s)
Latency A (ms) - Latency B (ms)

Fig. 3. Calculation of nerve conduction velocity (NCV). A horizontal line represents a nerve stimulated proximally at A and distally at B, with recording electrodes at C. For segment BC, the sensory NCV is calculated by dividing the surface distance BC (in centimeters) by the latency of the sensory response from B (in milliseconds). Multiplying by 10 converts centimeters/millisecond to meters/second. The motor NCV cannot be calculated for segment BC (see text). For segment AB, sensory and motor NCVs are calculated by dividing the distance AB by the latency difference between A and B, and then multiplying by 10.
m/sec by age 3 to 5 years (11,22,51) (Fig. 9). Normal values for infants and young children (11,39) are listed in Table 1.

**Late Responses**

Routine nerve conduction studies assess the distal and midportions of the peripheral nerve. Special studies that include conduction through the proximal or central nerve segments may reveal abnormalities not evident on routine studies. These tests are often classified as "late responses" because the response latencies are generally much longer than those obtained with conventional studies.

**Table 1. Range of normal values for nerve conduction studies in children**

<table>
<thead>
<tr>
<th></th>
<th>No. of subjects</th>
<th>Amplitude (mV/μV)</th>
<th>Conduction velocity (m/sec)</th>
<th>Distal latency (msec)</th>
<th>Distance (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonate</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Motor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulnar</td>
<td>58</td>
<td>1.6–7.0</td>
<td>20.0–36.1</td>
<td>1.3–2.9</td>
<td>1.0–3.4</td>
</tr>
<tr>
<td>Median</td>
<td>4</td>
<td>2.6–9.0</td>
<td>22.4–27.1</td>
<td>2.0–2.9</td>
<td>1.9–3.0</td>
</tr>
<tr>
<td>Peroneal</td>
<td>4</td>
<td>1.5–4.0</td>
<td>21.0–26.7</td>
<td>2.1–3.1</td>
<td>1.9–3.8</td>
</tr>
<tr>
<td>Sensory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>10</td>
<td>7–15 (A)</td>
<td>25.1–31.9</td>
<td>2.1–3.0</td>
<td>3.6–5.4</td>
</tr>
<tr>
<td>Sural</td>
<td>1</td>
<td>8–17 (O)</td>
<td></td>
<td>3.3</td>
<td>5.5</td>
</tr>
<tr>
<td>MedPlantar</td>
<td>3</td>
<td>10–40</td>
<td></td>
<td>2.1–3.3</td>
<td>4.4–5.8</td>
</tr>
<tr>
<td><strong>1–6 months</strong></td>
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<tr>
<td>Motor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulnar</td>
<td>22</td>
<td>2.5–7.4</td>
<td>33.3–50.0</td>
<td>1.1–3.2</td>
<td>1.7–4.4</td>
</tr>
<tr>
<td>Median</td>
<td>6</td>
<td>3.5–6.9</td>
<td>37.0–47.7</td>
<td>1.6–2.2</td>
<td>2.1–4.1</td>
</tr>
<tr>
<td>Peroneal</td>
<td>10</td>
<td>1.5–8.0</td>
<td>32.4–47.7</td>
<td>1.7–2.4</td>
<td>2.5–4.1</td>
</tr>
<tr>
<td>Sensory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>11</td>
<td>13–52 (A)</td>
<td>36.3–41.9</td>
<td>1.5–2.3</td>
<td>4.3–6.3</td>
</tr>
<tr>
<td>Sural</td>
<td>2</td>
<td>9–10</td>
<td></td>
<td>1.7–2.3</td>
<td>5.8</td>
</tr>
<tr>
<td>MedPlantar</td>
<td>2</td>
<td>17–26</td>
<td></td>
<td>1.5–1.9</td>
<td>4.5–5.5</td>
</tr>
<tr>
<td><strong>7–12 months</strong></td>
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<tr>
<td>Motor</td>
<td></td>
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</tr>
<tr>
<td>Ulnar</td>
<td>28</td>
<td>3.2–10.0</td>
<td>35.0–58.2</td>
<td>0.8–2.2</td>
<td>1.9–4.6</td>
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<tr>
<td>Median</td>
<td>13</td>
<td>2.3–8.6</td>
<td>33.3–46.3</td>
<td>1.5–2.8</td>
<td>1.9–4.3</td>
</tr>
<tr>
<td>Peroneal</td>
<td>19</td>
<td>2.3–6.0</td>
<td>38.8–56.0</td>
<td>1.4–3.2</td>
<td>2.2–5.5</td>
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<tr>
<td>Sensory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>15</td>
<td>14–64 (A)</td>
<td>39.1–60.0</td>
<td>1.6–2.4</td>
<td>5.5–6.8</td>
</tr>
<tr>
<td>Sural</td>
<td>5</td>
<td>10–26</td>
<td>40.3</td>
<td>1.7–2.5</td>
<td>5.8–7.6</td>
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<tr>
<td>MedPlantar</td>
<td>6</td>
<td>15–38</td>
<td>39.4–40.3</td>
<td>1.8–2.7</td>
<td>6.5–7.9</td>
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<td><strong>13–24 months</strong></td>
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<tr>
<td>Motor</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ulnar</td>
<td>53</td>
<td>2.6–6.7</td>
<td>41.3–63.5</td>
<td>1.1–2.2</td>
<td>2.4–4.8</td>
</tr>
<tr>
<td>Median</td>
<td>16</td>
<td>3.7–11.6</td>
<td>39.2–50.5</td>
<td>1.8–2.8</td>
<td>2.2–4.3</td>
</tr>
<tr>
<td>Peroneal</td>
<td>36</td>
<td>1.7–6.5</td>
<td>39.2–54.3</td>
<td>1.8–3.5</td>
<td>2.2–5.8</td>
</tr>
<tr>
<td>Sensory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>29</td>
<td>14–62 (A)</td>
<td>46.5–57.9</td>
<td>1.7–3.0</td>
<td>5.7–9.1</td>
</tr>
<tr>
<td>Sural</td>
<td>9</td>
<td>8–30</td>
<td></td>
<td>1.4–2.8</td>
<td>4.5–8.6</td>
</tr>
<tr>
<td>MedPlantar</td>
<td>12</td>
<td>15–60</td>
<td>42.6–57.3</td>
<td>1.8–2.5</td>
<td>6.1–6.3</td>
</tr>
</tbody>
</table>

With permission from ref. 39.
A, antidromic sensory potential; O, orthodromic sensory potential; MedPlantar, medial plantar nerve.
trodes used to measure the CMAP. Compared to the CMAP, the F wave has a smaller and more variable amplitude, a more variable waveform morphology, and a longer and more variable latency (Fig. 10). Because the F wave latency varies from trial to trial, multiple trials are performed and the shortest latency is reported.

The F wave conduction velocity (FWCV) provides the nerve conduction velocity along the segment from the stimulus site to the spinal cord. It is calculated using the following formula: FWCV = 2D/E – M – 1, where D is the distance from the stimulus site to the cord in millimeters, M (CMAP) and F are the respective wave latencies in milliseconds, and 1 represents an estimated 1 msec delay for turnaround time of the F wave at the anterior horn cell (20). For the upper extremities, D is measured from the C7 spinous process through the midclavicular line and axilla to the stimulus point. In the lower extremities, D is measured from the T12 spinous process through the greater trochanter of the femur to the stimulus site.

FIG. 9. Relationship of age and motor nerve conduction velocity (NCV) for the ulnar nerve elbow-to-wrist segment. Nerve conduction velocity values reach the adult range by approximately age 3 years. (With permission from ref. 51.)

FIG. 10. F wave responses. Eight sequential F wave responses following median nerve stimulation at the wrist are vertically displayed. The F wave response (arrow) has variable amplitude, latency, and waveform configuration. The waveform of the CMAP (far left) is not demonstrated well with the machine settings used to record the F wave.
**TABLE 2. F wave normal values**

<table>
<thead>
<tr>
<th>Nerve</th>
<th>F latency (msec)</th>
<th>FWCV (msec)</th>
<th>F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>22.8 ± 1.9 (27)</td>
<td>67.8 ± 5.8 (56)</td>
<td>0.98 ± .08 (0.82–1.14)</td>
</tr>
<tr>
<td>Ulnar</td>
<td>23.1 ± 1.7 (27)</td>
<td>65.7 ± 5.3 (55)</td>
<td>1.05 ± .09 (0.87–1.23)</td>
</tr>
<tr>
<td>Peroneal</td>
<td>39.9 ± 3.2 (46)</td>
<td>55.1 ± 4.6 (46)</td>
<td>1.05 ± .09 (0.87–1.23)</td>
</tr>
<tr>
<td>Tibial</td>
<td>39.5 ± 4.4 (48)</td>
<td>53.7 ± 4.8 (44)</td>
<td>1.11 ± .11 (0.89–1.33)</td>
</tr>
</tbody>
</table>

Sixty-one patients without known peripheral nerve disease, aged 11 to 75 years (mean age 40). Stimulation level is the elbow for the median and ulnar nerves and the knee for the peroneal and tibial nerves.

Values are mean plus 1 standard deviation (SD). Values in parentheses represent the upper normal limit (mean + 2 SD) for F wave latency, the lower normal limit (mean − 2 SD) for F wave conduction velocity (FWCV), and lower and upper normal limits for F ratio.

(Modified with permission from ref. 28A.)

Another measure, the F ratio, compares conduction time in the proximal nerve segment to the distal nerve segment when the nerve has been stimulated at a midlength location. The formula is \( F_{ratio} = \frac{F - M}{M - \frac{1}{2}M} \), where the M (CMAP) and F latencies are from the midlength stimulation site (20). This dimensionless ratio is close to one in the normal state. Increases in the F ratio indicate slow conduction in the proximal portion of the nerve; decreases indicate slowing in the distal nerve. Table 2 lists normal values for F wave studies. Values for infants and young children differ considerably from those for older children and adults (39).

**H Reflex.** The H reflex is a monosynaptic spinal reflex elicited by electrical stimulation of 1A afferent fibers. In the first year of life, the H reflex can be elicited in most nerves (39,52). In older children and adults, the H reflex can be routinely elicited only in the soleus and flexor carpi radialis muscle (16,29). In clinical practice, the H reflex is determined only in the calf muscle, providing information regarding the S1 reflex arc (Fig. 11). To elicit the H reflex, a submaximal, long-duration

![FIG. 11. The H reflex. A: The recording technique shows the active electrode placed just medial to the tibia at a point located half the distance from the tibial tubercle to the medial malleolus. The stimulus (not shown) is applied to the tibial nerve in the medial aspect of the popliteal fossa. B: The top tracing shows an isolated H reflex response obtained with a low-intensity, long-duration stimulus. With increasing stimulus intensity on successive traces, the H reflex is preceded by a CMAP, which increases in amplitude as the H reflex response decreases in amplitude.](image-url)
(1 msec) stimulus is given to the tibial nerve in the popliteal fossa. This permits selective activation of the 1A sensory fibers without activating motor fibers. As the stimulus intensity is gradually increased, the H reflex amplitude increases, and a CMAP is also recorded (Fig. 11). Further increases in intensity cause the CMAP amplitude to increase and the H reflex amplitude to decrease.

The parameters assessed for the H reflex include amplitude and latency. The H reflex is recorded bilaterally, and the results of the two sides are compared. Normal values are given in Table 3. The major role of the H reflex is in the assessment of an S1 radiculopathy. Bilateral absence, or prolongation of H reflex latency by 1.5 msec compared to the normal side, indicates an abnormality in the S1 reflex pathway and supports a diagnosis of S1 radiculopathy. However, an abnormal H reflex is not diagnostic of S1 radiculopathy, as it may be absent indefinitely after remote S1 radiculopathy and may be absent bilaterally in polyneuropathy and in persons over age 60 (56).

Blink Reflex. Review of the well-known corneal reflex helps introduce the blink reflex. Stimulation of the cornea with a wisp of cotton results in a reflex blink of both eyes. The afferent portion of this reflex is mediated by the ipsilateral trigeminal nerve, and the efferent portion is mediated by the facial nerve bilaterally. The blink reflex is similar but involves an electric stimulus and quantification of the response.

<table>
<thead>
<tr>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. IIth Nerve</td>
</tr>
<tr>
<td>2. IIIth Nerve</td>
</tr>
<tr>
<td>3. Main Sensory Nucleus</td>
</tr>
<tr>
<td>4. Spinal Nucleus</td>
</tr>
<tr>
<td>5. Uncrossed Interneurons</td>
</tr>
<tr>
<td>6. Crossed Interneurons</td>
</tr>
</tbody>
</table>

![supraorbital nerve](image)

**Fig. 12.** The blink reflex. Bilateral, simultaneous recordings from the orbicularis oculi muscles are displayed as pairs of traces. The top tracing of each pair is the recording ipsilateral to the supraorbital nerve stimulus, and the bottom tracing is the contralateral recording. The normal response shows an early potential called R1, which occurs only on the side ipsilateral to the stimulus. Subsequently, there are multiphasic potentials collectively called R2, which occur bilaterally. Patterns of blink reflex abnormalities, numbered 1 through 6, suggest a conduction disturbance involving the trigeminal nerve in 1; the facial nerve in 2; the trigeminal main sensory nucleus in 3; the trigeminal spinal tract in 4, uncrossed medullary interneurons to the ipsilateral facial nucleus in 5; and crossed medullary interneurons to the contralateral facial nucleus in 6. (With permission from ref. 28.)

### Table 3. H reflex normal values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude (mV)</td>
<td>2.4 ± 1.4</td>
</tr>
<tr>
<td>Amplitude difference (mV)</td>
<td>1.2 ± 1.2</td>
</tr>
<tr>
<td>Latency (msec)</td>
<td>29.5 ± 2.4 (mean)</td>
</tr>
<tr>
<td>Latency difference (msec)</td>
<td>0.6 ± 0.4 (1.4 mean)</td>
</tr>
<tr>
<td>Right-left sides (msec)</td>
<td></td>
</tr>
</tbody>
</table>

Fifty-nine patients without known peripheral nerve disease, aged 11 to 78 years (mean age 39). Values are mean ± 1 standard deviation (SD). Values in parentheses represent the upper normal limit (mean ± 2 SD).
TABLE 4. Latency values for facial nerve CMAP and blink reflex

<table>
<thead>
<tr>
<th></th>
<th>Number averaged</th>
<th>Direct response (msec)</th>
<th>R1 (msec)</th>
<th>R/D ratio</th>
<th>Ipsilateral R2 (msec)</th>
<th>Contralateral R2 (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal adults</td>
<td>186</td>
<td>2.9 ± 0.4</td>
<td>10.5 ± 0.8</td>
<td>3.6 ± 0.5</td>
<td>30.5 ± 3.4</td>
<td>30.5 ± 4.4</td>
</tr>
<tr>
<td>Normal neonates</td>
<td>90</td>
<td>3.3 ± 0.4</td>
<td>12.1 ± 1.0</td>
<td>3.7 ± 0.4</td>
<td>35.9 ± 2.5</td>
<td>Often absent</td>
</tr>
<tr>
<td>Diabetic polyneuropathy</td>
<td>172</td>
<td>3.4 ± 0.6</td>
<td>11.4 ± 1.2</td>
<td>3.4 ± 0.5</td>
<td>33.7 ± 4.6</td>
<td>34.8 ± 5.3</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>108</td>
<td>4.5 ± 3.4</td>
<td>15.1 ± 6.9</td>
<td>3.8 ± 1.0</td>
<td>38.2 ± 6.9</td>
<td>38.3 ± 6.7</td>
</tr>
<tr>
<td>Charcot-Marie-Tooth disease</td>
<td>92</td>
<td>5.7 ± 3.1</td>
<td>15.7 ± 4.1</td>
<td>3.1 ± 1.0</td>
<td>38.5 ± 6.7</td>
<td>38.6 ± 6.5</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>126</td>
<td>2.9 ± 0.5</td>
<td>12.3 ± 2.7</td>
<td>4.3 ± 0.9</td>
<td>35.8 ± 6.4</td>
<td>35.7 ± 6.0</td>
</tr>
</tbody>
</table>

With permission from ref. 21. Values are mean ± standard deviation.

Interpreting blink reflex results requires knowledge of the status of the facial nerves. The facial nerve is electrically stimulated just anterior to the mastoid process, and the CMAP is recorded from the ipsilateral nasalis muscle. Side-to-side comparison of facial nerve CMAP amplitudes may reveal unilateral facial nerve axonal degeneration. Facial nerve conduction study and blink reflex results for normals and several disease states are summarized in Table 4.

INTERPRETATION

Traditional Classification of Nerve Injury

Seddon’s classification of nerve injuries into three major categories: neuropaxia, axonotmesis, and neurotmesis. Neuropaxia indicates impaired nerve function due to failure of impulse conduction without any structural change involving the axons. It is the type of injury that occurs with mild to moderate acute compressive nerve injuries. The pathophysiology of neuropaxic nerve injury may be either acute nerve ischemia or parapinal demyelination (43). Because axons remain intact and Schwann cells can reestablish myelin, recovery from a neuropaxic injury is generally excellent. The time for recovery is generally weeks to months.

Axonotmesis refers to a nerve injury causing interruption of axons but sparing the nerve’s connective tissues. It is often caused by a crush injury to a limb. The axons distal to the site of injury subsequently undergo wallerian degeneration. Because the connective tissues remain intact, regenerating axons can grow within intact Schwann cell tubes to reestablish appropriate connections. Recovery from axonotmesis is generally good. However, because axonal regeneration proceeds at a rate of about 1 to 3 mm per day (24), the time for recovery is many months.

Neurotmesis indicates a more severe injury in which both axons and the nerve’s connective tissues are disrupted. As in axonotmesis, axons distal to the site of injury undergo wallerian degeneration. Recovery from neurotmesis is generally poor because dissociation of Schwann cell tubes eliminates the conduit to guide regenerating axons to the appropriate destination. Surgical reanastomosis of the transected nerve is necessary for nerve regrowth to occur. Even then, however, functional recovery is frequently poor because there is no mechanism to guide regenerating axons to reestablish their original sensory and motor connections (49,50).

Electrophysiologic Classification of Nerve Injury

Seddon’s classification of nerve injuries remains useful for understanding the pathophysiologic mechanisms of physical nerve injury and for predicting prognosis. However, for several reasons, it cannot be routinely applied to the broad spectrum of neuromuscular disorders seen in the clinical electrophysiology laboratory. First, similar electrophysiologic abnormalities may occur secondary to many other causes of nerve dysfunction, such as hereditary or acquired metabolic neuropathies, or from other neuromuscular disorders, such as anterior horn cell disorders, neuromuscular transmission disorders, or primary muscle diseases. In these conditions, the prognosis for recovery may be far less predictable than for physical nerve injuries. Second, a demyelinating nerve injury and a neuropaxic nerve injury are not the same. Neuropaxia specifically indicates conduction block, which is one of several electrophysiologic findings of demyelinating nerve injury. Some neuropathies typically regarded as demyelinating, such as the hereditary motor sensory neuropathies, do not have evidence of conduction block and are not considered neuropaxic (33). Finally, a distinction between axonotmesis and neurotmesis cannot always be made with electrophysiologic techniques. Axonal injury produced by either severe axonotmesis or neurotmesis causes similar electrophysiologic abnormalities.

Thus, when nerve conduction study results are ab-
normal, it is generally not helpful to make an interpretation based on Seddon’s classification. Rather, the first step is to correlate those findings with the patient’s clinical condition, which will usually reveal whether the patient has peripheral nerve disease and whether it is focal (mononeuropathy) or diffuse (polyneuropathy). Next, the type of nerve injury is classified as demyelinating or axonal, based on the electrophysiologic findings discussed below. This distinction cannot be made by clinical features and is essential for determining the focus of subsequent diagnostic investigations.

Demyelinating Injury

Manifestations of a demyelinating nerve injury can be divided into waveform changes and latency changes. Waveform changes refer to alterations in the appearance of the response waveform and consist of conduction block and temporal dispersion. Latency changes consist of prolonged latencies and slow nerve conduction velocities. To appreciate these electrophysiologic changes, it is necessary to review the physiologic consequences of demyelination.

Saldatory conduction of impulses in myelinated fibers depends on the depolarizing NAP current jumping from node to node across individual myelin segments. Loss of myelin from peripheral nerve fibers with saldatory conduction of impulses through the region of demyelination. The depolarizing current dissipates in the demyelinated region and either becomes insufficient to depolarize subsequent nerve segments or does so in a much delayed fashion (31). The electrophysiologic manifestations of these two outcomes are conduction block when the impulse fails to conduct entirely and temporal dispersion, prolonged response latencies, and slow nerve conduction velocities when the impulse is delayed in the demyelinated region. The functional and electrophysiologic outcomes of demyelination are determined by how severely individual axons are demyelinated, the number of axons affected at a given site of demyelination, and the number of sites along the course of the nerve that are demyelinated.

Conduction block, also called neurapraxia, indicates that an impulse fails to propagate along an intact axon. Because axons remain functional in a purely demyelinating nerve injury, the nerve conducts impulses normally when stimulated distal to the region of demyelination. Electrical stimulation of the same nerve proximal to the site of demyelination yields responses that are reduced in amplitude and area proportional to the number of fibers in which impulses are blocked (Fig. 13). The number of fibers with blocked conduction can be estimated by comparing the amplitude of the proximal and distal responses. A proximal to distal amplitude ratio of 0.7, suggesting that 30% of fibers are blocked, has been cited as an acceptable degree of change to be called conduction block (1). Others use a ratio of 0.5 to diagnose conduction block (33).

However, a proximal to distal amplitude ratio of less than one should not be interpreted as absolute evidence of conduction block, because both physiologic and technical factors may produce this finding. A physiologic factor contributing to smaller-amplitude responses with proximal, compared to distal stimulation, is physiologic temporal dispersion (23). In many normal individuals, physiologic temporal dispersion accounts for reduction in amplitude of antidromic SNAPs recorded from a digit when an upper-extremity nerve is stimulated in the axilla. In contrast, the amplitude of CMAPs obtained with proximal stimulation is affected only slightly by physiologic temporal dispersion. For this reason, assessment of conduction block is done routinely only for motor fibers. Conduction block can certainly occur in sensory fibers, however, and can sometimes be demonstrated electrophysiologically (12).

When conduction is slowed through a demyelinated region, the degree of temporal dispersion exceeds that which occurs physiologically. The action potentials of individual axons arrive at the recording electrodes in an excessively desynchronized fashion. This produces a temporally dispersed—appearing CMAP characterized by relatively low amplitude and long duration compared to the CMAP waveform obtained with distal stimulation (Fig. 13). In addition, the CMAP's smoothly contoured monophasic negative waveform is often replaced by a rough appearing waveform with multiple phases. When temporal dispersion is present, the action potentials of some nerve fibers may arrive

![Figure 13: Conduction block and temporal dispersion.](image-url)

Ulnar motor nerve conduction study in a patient with a demyelinating polyneuropathy shows the compound muscle action potential (CMAP) obtained after stimulating the ulnar nerve at the wrist, below the elbow, above the elbow, and at the axilla. With proximal stimulation sites, the CMAP has a relatively smaller amplitude, and the waveform becomes desynchronized into multiple low-amplitude phases (temporal dispersion).
at the recording electrodes out of phase, resulting in nullification. This event, termed phase cancellation, gives the electrophysiologic appearance of a reduced or absent action potential. For this reason, when temporal dispersion is present, it is not possible to know how many nerve fibers have failed to conduct (conduction block) and how many have desynchronized conduction (temporal dispersion) resulting in phase cancellation. This uncertainty poses no practical difficulty because true conduction block and temporal dispersion are seen only in demyelinating nerve injury, not axonal injury. In the case of polyneuropathy, conduction block suggests that a demyelinating nerve injury is acquired, since it is usually not seen in hereditary demyelinating polyneuropathies (31,33). Technical factors mimicking conduction block are discussed later in the section concerning the pitfalls of nerve conduction studies.

Other features of demyelinating nerve injury, including slow nerve conduction velocities and prolonged latencies, occur as a consequence of slow conduction through demyelinated regions. Because axonal degeneration of fast-conducting fibers can reduce the velocity to 70% to 80% of the lower normal limit (32), the degree to which demyelination causes slow velocities depends on the number of fast-conducting fibers contributing to the response. The amplitude of the CMAP obtained with distal stimulation provides an indication of how many fast-conducting fibers are present. If the distal CMAP amplitude exceeds 50% of the lower normal limit, loss of fast-conducting fibers should not contribute substantially to slowing. In this setting, nerve conduction velocity values below 80% of the lower normal limit suggest demyelination (32). If the distal CMAP amplitude is considerably less than 50% of the lower normal limit, loss of fast-conducting fibers likely contributes to slow velocities, and values must reach less than 70% of the normal lower limit to suggest demyelination (32). Similar considerations apply to prolonged distal latencies. An attempt to quantify the changes that constitute demyelination has been made for the acquired demyelinating polyneuropathies (1).

Axonal Injury

With supramaximal nerve stimulation, SNAP and CMAP amplitudes are proportional to the number of conducting axons. Axonal injury and subsequent degeneration reduce the number of conducting axons, causing the SNAP and CMAP amplitudes to decline. Depending on the nature and severity of the disorder causing nerve injury, there may be selective involvement of sensory or motor fibers. Unlike a proximal demyelinating nerve injury, which preserves the amplitude of the CMAPs and SNAPs obtained with distal stimulation and axonal nerve injury causes reduced-amplitude responses with distal stimulation. However, an acute axonal nerve injury may mimic a demyelinating process. Nerve conduction studies are performed in the first week following the injury. In this time frame, the amplitude of the CMAPs and SNAPs obtained with stimulation distal to the site of injury may be normal, because axons have not yet degenerated and continue to conduct impulses. Because the CMAP obtained with stimulation proximal to the site of injury is reduced or absent, this pattern resembles conduction block. If the studies are repeated 7 to 10 days after the injury, axonal degeneration will have occurred, and the responses with distal stimulation will be lost or reduced.

As a general rule, slowing of nerve conduction velocity with axonal nerve injury is mild compared to that seen with demyelinating nerve injury. Loss of large numbers of fast-conducting fibers may reduce the velocity to 70% to 80% of the lower normal limit (32). If roughly 50% or more of the fast-conducting fibers remain, slowing of nerve conduction velocity due to axonal injury is estimated to result in a velocity that is 80% to 90% of the lower normal limit (32).

The other major finding with axonal injury of motor fibers is evidence of muscle fiber denervation on the needle exam (EMG). Fibrillation potentials develop in muscles about 7 to 10 days after axonal injury (4). Fibrillation potentials do not occur in purely demyelinating nerve lesions, but they may be seen when a primarily demyelinating nerve lesion has associated axonal degeneration.

The electrophysiologic changes of axonal injury are seen with either axonotmesis or neurotmesis. If CMAPs and SNAPs are completely lost immediately following axonal nerve injury, it cannot be determined whether this represents severe axonotmesis or neurotmesis. If reduced-amplitude CMAPs and/or SNAPs continue to be obtained many weeks after the onset of nerve injury, neurotmesis can be excluded, as this would be expected to produce complete loss of responses. An exception occurs in nerve root avulsion, in which case the SNAPs remain normal despite neurotmesis (53). This occurs because the injury involves the preganglionic dorsal root ganglion fibers. The postganglionic dorsal root ganglion fibers, which are assessed with sensory nerve conduction studies remain in continuity with the dorsal root ganglion and function normally.

Other Causes of Abnormal Nerve Conduction Studies

In addition to primary peripheral nerve disease, other neuromuscular disorders may produce abnormal
results. Because the abnormalities associated with these disorders overlap, it is imperative to analyze the patient's clinical features during the interpretation process. The findings produced by various neuromuscular disorders can be organized by analyzing the M- and SNAPs affected.

Reduced-amplitude CMAPs may be seen with anterior horn cell disorders, radiculopathies, plexopathies, certain neuropathologic transmission disorders, and some myopathies. With anterior horn cell disorders, radiculopathies, plexopathies, and neuropathies, reduced-amplitude CMAPs are caused by axonal degeneration of motor nerve fibers. With neuromuscular transmission disorders and myopathies, motor nerve axons are generally normal, and the reduced-amplitude CMAPs result from disease involving the neuromuscular junction and the muscle fiber, respectively.

As a general rule, SNAPs remain normal in anterior horn cell disease, radiculopathies, neurofascicular transmission disorders, and myopathies. Despite sensory involvement in radiculopathies, the SNAP remains normal because the preganglionic site of pathologic lesions is the dorsal root ganglion and peripheral nerve fibers. With anterior horn cell disorders, neurofascicular transmission disorders, and myopathies, the underlying disease process spares the peripheral sensory system. Plexopathies and neuropathies are the only categories of neuromuscular diseases that show reduced amplitude of both CMAPs and SNAPs.

Regardless of the site of axonal injury, slowing of nerve conduction velocity is possible when large numbers of fast-conducting fibers are lost. Thus, slowing of motor nerve conduction velocity may be seen in anterior horn cell disorders, radiculopathies, and plexopathies as well as in peripheral nerve disease. Slowing of sensory nerve conduction velocity may occur in plexopathies and neuropathies.

**Pitfalls of Nerve Conduction Studies**

The basic principles and methods for performing nerve conduction studies are straightforward, but there are numerous potential problems when attempting such methods. Wilbourn aptly summarized these difficulties by stating, "What superficially appears to be an easy task is fraught with a myriad of problems and potential errors...anatomical, technical, procedural, and interpretative in nature...which represent a formidable barrier to the performance of accurate, reproducible and therefore, clinically reliable studies." The pitfalls encountered with nerve conduction studies can be divided into two broad categories: physiologic and technical.

**Physiologic Factors**

Physiologic factors affecting the interpretation of nerve conduction studies include patient age, limb temperature, and nerve abnormalities. Although age does not affect results in young and middle-aged adults, it may have a major effect on tests involving the very young and the elderly. For premature infants, nerve conduction velocities are very slow—for example, 17 to 25 m/sec for the ulnar nerve (5). Full-term infants have nerve conduction velocity values of 21 to 29 m/sec for the ulnar nerve (51). Adult values (approximately 50 to 70 m/sec) are reached by age 3 to 5 years (17,27,51) (Fig. 9). By the sixth to eighth decades of life, nerve conduction velocities decrease by less than 10 m/sec compared to young-adult values (40). A more common problem with individuals over the age of 60 is loss of lower-extremity SNAPs and H reflex responses (55). Care must be taken to avoid interpreting age-related findings as abnormal.

Temperature may profoundly affect nerve conduction study results because cool temperatures prolong latencies and slow nerve conduction velocities. The nerve conduction velocity of the median and ulnar nerves has been shown to change linearly by 2.4 m/sec per degree C over the temperature range of 29 to 38 degrees C (13). Median and ulnar nerve wrist latencies increase by 0.3 m/sec per degree C when the hand is cooled (22). To avoid interpretative error, skin temperature should be measured before beginning the study; if it is less than 32 degrees C, the patient should be warmed. An alternative approach is to attempt to adjust the nerve conduction velocity values for temperature by adding 3% of the calculated velocity for each degree below 34 degrees C (22).

Anomalus muscle innervation may create confusion when analyzing nerve conduction study results. The most commonly observed anomaly in the electromyography laboratory is the Martin-Gruber anastomosis, in which nerve fibers traveling with the median nerve in the arm cross to the ulnar nerve in the forearm. These median-to-ulnar fibers may innervate hypothenar and thenar muscles and the first dorsal interosseous muscle. If a Martin-Gruber anastomosis innervates the hypothenar eminence, a routine ulnar nerve conduction study may give the false appearance of conduction block of the ulnar nerve in the elbow region. Awareness of this anomaly can produce this finding should lead to additional studies to determine if it is indeed present (19).

**Technical Factors**

Technical factors affecting nerve conduction study results can be divided into those concerning stimul-
tion, recording, and measuring. A common problem is uncertainty that a supramaximal nerve stimulus has been delivered to a nerve that is deep beneath intervening tissues. This vexing problem occurs frequently when attempting to stimulate the brachial plexus at Erb's point or the tibial nerve at the knee. Other nerves may be difficult to stimulate if local factors such as edema, adipose tissue, scarring, or other skin changes are present. Because it is generally easier to stimulate a nerve supramaximally in its distal portion, care must be taken not to diagnose conduction block when inadequate stimulation of the proximal portion of the nerve causes a relatively reduced CMAP.

Spread of the stimulating current to activate nerves other than the one intended is another potential source of error (19,22). This may occur when nerves travel closely together (e.g., the median and ulnar nerves in the axilla) or when stimulus intensity is increased to high levels (despite substantial anatomic separation of nerves). In these settings, attributing a response to the wrong nerve may cause diagnostic error.

Potential pitfalls in recording nerve responses include improper placement of recording electrodes, incorrect instrument settings (48), and measurement errors. Reliance on computer identification of responses is fraught with error. Calculation of nerve conduction velocities may be inaccurate because the nerve segment distances are estimated from the skin surface rather than measured precisely (22).

Recognition of the many potential pitfalls encountered in performing nerve conduction studies is necessary to avoid erroneous conclusions. If a technical problem cannot be eliminated, at least exposing its presence serves to minimize its consequences.

NEUROMUSCULAR TRANSMISSION

Anatomy

The neuromuscular junction is a cholinergic synapse consisting of a presynaptic portion, the nerve terminal; a postsynaptic portion, the muscle end plate; and the intervening space, the synaptic cleft. The nerve terminal is an ovoid-shaped ending of a motor axon. It contains abundant synaptic vesicles, mitochondria, cisternal structures, and cytoskeletal elements (9). Synaptic vesicles contain the neurotransmitter acetylcholine. Vesicles are clustered around specialized presynaptic membrane sites called active zones. Here, vesicles attach and release acetylcholine into the synaptic cleft. The active zones are located in close approximation to regions of the postsynaptic membrane where acetylcholine receptors are highly concentrated. The postsynaptic end plate region is convoluted into folds, with crests of folds containing numerous acetylcholine receptors. The number of receptors is estimated to be $1.5 \times 10^9$ per end plate (34). Acetylcholine receptors are glycoproteins composed of several subunits traversing the postsynaptic membrane. They have at least two binding sites for acetylcholine and separate sites for binding other molecules (34). The 50-nanometer synaptic cleft contains a ground substance and the enzyme acetylcholinesterase, which hydrolyzes acetylcholine.

Physiology

Acetylcholine is synthesized in the presynaptic terminal from choline and acetylcoenzyme A by the enzyme choline acetyltransferase. Acetylcholine is actively taken up into vesicles, where it is stored. At rest, acetylcholine is released spontaneously when vesicles fuse with the presynaptic membrane and release their contents. The amount released from a vesicle, called a quantum, consists of between 5,000 and 10,000 acetylcholine molecules (27,34,36). When two molecules of acetylcholine bind to an acetylcholine receptor, a configurational change in the receptor molecule takes place, allowing a centrally located ion channel to open for a few milliseconds (17,36). As a result, sodium ions travel intracellularly down their electrochemical gradient, producing a brief nonpropagated depolarization of the postsynaptic membrane. The membrane depolarization produced by a single quantum of acetylcholine is called a miniature end plate potential (MEPP).

When a MEPP reaches the nerve terminal, the depolarization results in an influx of calcium ions into the nerve terminal. This increased presynaptic calcium accelerates the rate of vesicle fusion with the presynaptic membrane and causes a synchronized release of approximately 100 to 300 quanta (27,36). The postsynaptic effect of the synchronized release of quanta can be viewed as summation of many individual MEPPs, resulting in a larger potential called the end plate potential (EPP). The EPP is a graded response proportional to both the number of acetylcholine quanta released and the number of functional acetylcholine receptors. The EPP does not spread throughout the muscle fiber but remains confined to the end plate region. If the EPP reaches a high enough level, called the threshold, an MFAP is generated that propagates along the muscle fiber membrane. The amount of depolarization necessary to reach threshold in the normal state is between 10 and 30 mV (22). The fact that an MFAP does not occur unless the threshold level of depolarization is achieved is referred to as the "all or none" property of muscle. Through a process known as excitation-contraction coupling (Chapter 56A), the MFAPs lead to contraction of the myofibrils, which make up the muscle fiber.
In normal individuals, the number of acetylcholine molecules released in response to a NAP is three to four times greater than necessary for the EPP to reach threshold (15). This more-than-adequate interaction of acetylcholine molecules and receptors has been referred to as the “safety factor” of neuromuscular transmission (54). Disease processes can reduce the safety factor by decreasing the amount of acetylcholine that is released or available to be released, decreasing the ability of acetylcholine to interact with the receptor, or decreasing the number of functional receptors. If a NAP arriving at the nerve terminal does not produce an EPP large enough to reach threshold, then an MFAP does not occur and the MFAP is said to have “blocked” (Fig. 14). In normal individuals, a supramaximal nerve stimulus will elicit an MFAP in all muscle fibers supplied by the nerve; the summed voltage change of these individual MFAPs, measured by a surface electrode overlying the muscle belly, produces a CMAP. In neuromuscular transmission disorders, blocking of MFAPs reduces the area and amplitude of the CMAP.

The vesicles in the presynaptic region are not all readily available for release. They behave as if they are segregated into three functional compartments (17,27,54). The first or primary store contains approximately 1,000 quanta located adjacent to the active sites of the presynaptic membrane. These quanta are immediately available for release in response to a NAP. The second store contains roughly 10,000 quanta. These quanta function as a mobilization store and readily replenish the primary store quanta after they are released. Quanta begin moving from the mobilization store to the primary store in 1 to 2 seconds; by 5 to 10 seconds, the process is complete (27). The third or main store of acetylcholine contains about 300,000 quanta, which are thought to be released to the mobilization store when there is a prolonged stimulus to the nerve.

**Repetitive Nerve Stimulation**

After a single NAP, the increased presynaptic calcium concentration persists for about 200 ms before calcium ions diffuse out of the presynaptic terminal (27). If a second NAP reaches the nerve terminal before the diffusion of presynaptic calcium ions occurs, then a greater percentage of the remaining acetylcholine will be released. Multiple NAPs arriving at the nerve terminal in succession, either by repetitive nerve stimulation or by continued voluntary activity, influence the release of acetylcholine via two opposing mechanisms: increased presynaptic calcium concentration facilitates acetylcholine release, and depletion of acetylcholine in the immediately available store diminishes acetylcholine release. How these opposing mechanisms affect acetylcholine release depends on the rate of nerve stimulation.

Because calcium diffusion out of the presynaptic terminal is complete at 200 ms after a NAP, stimuli with an interstimulus interval greater than 200 ms (rate < 5 Hz) are not associated with calcium-dependent facilitation of acetylcholine release. Stimuli at rates exceeding 5 Hz cause calcium-dependent facilitation of acetylcholine release, especially when stimulus rates of 20 to 50 Hz are used. Because acetylcholine mobilization takes at least 1 second to begin, stimuli with an interstimulus interval of less than 1,000 ms (rate > 1 Hz) allow the second stimulus to arrive before significant acetylcholine mobilization has occurred. Thus, stimulation at rates of 1 to 5 Hz depletes the immediately available acetylcholine store without causing calcium-dependent facilitation of acetylcholine release. In normal individuals, repetitive nerve stimulation at rates of 1 to 5 Hz reduces the immediately available acetylcholine store. However, the abundant acetylcholine released and the normal number of receptors available (safety factor) allow the EPP to reach threshold in all muscle fibers. Thus, repetitive nerve stimulation in normal individuals produces no change in the amplitude of the CMAP. In patients with neuromuscular transmission disorders, depletion of the immediately available acetylcholine store may reduce the safety factor sufficiently so that the EPP in some mus-
nucle fibers does not reach threshold and, consequently, an MFAP does not occur in these fibers (blocking).

When repetitive nerve stimulation is performed at a slow rate (e.g., 3 Hz) in patients with neuromuscular transmission disorders, reduction of the size and area of the CMAP due to blocking of some MFAPs produces a characteristic pattern called a decremental response \((15,17,27,37)\) (Fig. 15). When repetitive nerve stimulation is performed in patients with neuromuscular transmission disorders at a fast rate (e.g., 20 to 50 Hz) or immediately after exercising the muscle being tested, an increase in the size and area of the CMAP, called an incremental response, may be seen \((15,17,27,37)\). This is caused by calcium-dependent facilitation of acetylcholine release. The increment in Lambert-Eaton myasthenic syndrome is typically greater than 100%; in botulism it may be less \((17,37)\). An increment may be seen in myasthenia gravis \((38)\), but this is only rarely greater than 100% \((46)\). More commonly in myasthenia gravis, exercise causes partial or complete correction (repair) of the previously noted decrement \((15)\). The increment in Lambert-Eaton syndrome and the repair seen in myasthenia gravis last only about 30 seconds \((27)\). In contrast, the increment in botulism is sustained for many minutes. This is a unique feature of botulism called prolonged posttetanic facilitation \((10)\).

The selection of muscles for repetitive nerve stimulation study is critical in myasthenia gravis as proximal muscles have a much higher yield of abnormality than distal ones. This consideration seems less important for Lambert-Eaton syndrome. In suspected botulism, multiple muscles must be assessed with repetitive nerve stimulation, as abnormalities are not uniform \((15)\).

REFERENCES


