

Single fiber EMG and measuring jitter with concentric needle electrodes

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Abstract

This monograph contains descriptions of the single-fiber electromyography (SFEMG) method and of the more recently implemented method of recording jitter with concentric needle electrodes (CNE). SFEMG records action potentials from single muscle fibers (SFAPs), which permits measuring fiber density (FD), a sensitive measure of reinnervation, and jitter, a sensitive measure of abnormal neuromuscular transmission (NMT). With voluntary activation, jitter is measured between two SFAPs with acceptable amplitude and rise time. With activation by axon stimulation, jitter is measured between the stimulus and individual SFAPs. Pitfalls due to unstable triggers and inconstant firing rates during voluntary activation and subliminal stimulation during axon stimulation should be identified and avoided. In CNE recordings, spikes with shoulders or rising phases that are not parallel are produced by summation of SFAPs; these should be excluded and reference values for CNE jitter should be used. CNE and SFEMG have similar and very high sensitivity in detecting increased jitter, as in myasthenia gravis and other myasthenic conditions. However, jitter is also seen in ongoing reinnervation and some myopathic conditions. With SFEMG, these can be identified by increased FD; however, FD cannot be measured with CNE, and conventional EMG should be performed in muscles with increased jitter to detect neurogenic or myogenic abnormalities. Jitter is abnormal after injections of botulinum toxin, even in muscles remote from the injection site, and can persist for 6 mo or more. This can complicate the detection or exclusion of abnormal NMT.

KEYWORDS

concentric needle electrodes, jitter, myasthenia gravis, neuromuscular transmission, single fiber EMG

Abbreviations: AP, action potential; ASFAP, apparent single-fiber action potential; BoNT, botulinum neurotoxin; CMS, congenital myasthenic syndrome; CNE, concentric needle electrode; CPEO, chronic progressive external ophthalmoplegia; ED, extensor digitorum; EMG, electromyography; EPP, endplate potential; FD, fiber density; IDI, interdischarge interval; IPI, interpotential interval; LEMS, Lambert–Eaton myasthenic syndrome; MCD, mean value of consecutive differences; MG, myasthenia gravis; MMG, MG patients with anti-MuSK antibodies; MSD, mean sorted-data difference; MUP, motor unit potential; MuSK, muscle-specific tyrosine kinase; NMJ, neuromuscular junction; NMT, neuromuscular transmission; OO, orbicularis oculi; RNS, repetitive nerve stimulation; SFAP, single-fiber action potential; SFE, single-fiber electrode; SFEMG, single-fiber electromyography; SPACE, stimulated potential analysis using concentric needle electrode; VRF, velocity recovery function.

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1 | SINGLE-FIBER ELECTROMYOGRAPHY: RECORDING PRINCIPLES AND ANALYSIS

Single-fiber electromyography (SFEMG) is a selective electromyography (EMG) recording technique that identifies action potentials (APs) from individual muscle fibers.¹ The selectivity of the technique results from the small recording surface (25 μm in diameter), which is exposed at a port on the side of the electrode, 3 mm from the tip (Figure 1). The selectivity of the recording is further enhanced by using a 500 Hz high-pass filter. Because signals from distant muscle fibers contain relatively more low-frequency activity than those from muscle fibers close to the recording electrode, filtering the low-frequency components reduces the contribution from distant muscle fibers. Identifying APs from individual muscle fibers by SFEMG allows the measurement of two features of the motor unit: fiber density (FD) and the neuromuscular jitter.

1.1 | Fiber density

The amplitude of APs recorded with a single-fiber electrode (SFE) from an average muscle fiber decreases to 200 μV when the electrode is approximately 300 μm from the muscle fiber. Thus, it can be inferred that APs with amplitudes greater than 200 μV and rise times less than 300 μs are generated by muscle fibers within 300 μm of the recording surface. Measuring the mean number of time-locked APs with amplitudes greater than 200 μV in many sites within a muscle, allows calculation of the FD, which quantifies the local concentration of muscle fibers within the motor unit. This information is analogous to fiber-type grouping in muscle biopsies. The FD is a sensitive means of detecting and quantifying rearrangement of the muscle fiber topography within the motor unit; FD is increased in neuropathies and some myopathies.

FD measurements are made while observing the EMG signals on the display screen. As the patient voluntarily activates the tested muscle, the electrode is positioned to record with maximum amplitude the AP from one muscle fiber. This AP triggers the display and is delayed so that the

number of synchronized APs with amplitudes over 200 μV and acceptable rise times can be counted. Counts are made in 20 sites within a muscle, usually via 2 or 3 separate skin insertions. The FD is the mean number of APs, including the triggering AP, in these 20 sites. Care must be taken to count as separate APs any that are partially obscured by other APs; if there is a clear "notch" between 2 such potentials, they are counted as separate APs, even if the amplitude of the smaller AP is <200 μV . FD normative values for many muscles have been determined.² They differ among various muscles and increase with age, especially after age 70 y. These age-dependent changes are more marked in some muscles than others, especially in distal muscles. In people whose occupation involves chronic muscle use, these age-dependent changes are more marked, suggesting that age and chronic use produce mild denervation and reinnervation.

1.2 | Neuromuscular jitter

When APs recorded with an intra- or extracellular electrode are elicited by nerve stimulation, the latency from stimulus to response varies (Figure 2). This variation is the neuromuscular jitter, which is produced by fluctuations in the time for endplate potentials (EPPs) to reach the AP threshold. Jitter is increased whenever the ratio between the EPP amplitude and AP threshold is less than normal. This means that the slope of the EPP is less steep than normal, which increases the variability of the time of AP activation. Thus, jitter is a sensitive measure of the *safety factor of neuromuscular transmission* (NMT). Jitter can be measured either while the axon is stimulated or the patient voluntarily activates the muscle.

1.3 | Jitter measurements during axonal stimulation

Jitter studies made with axonal stimulation are particularly useful when the patient has difficulty maintaining constant voluntary

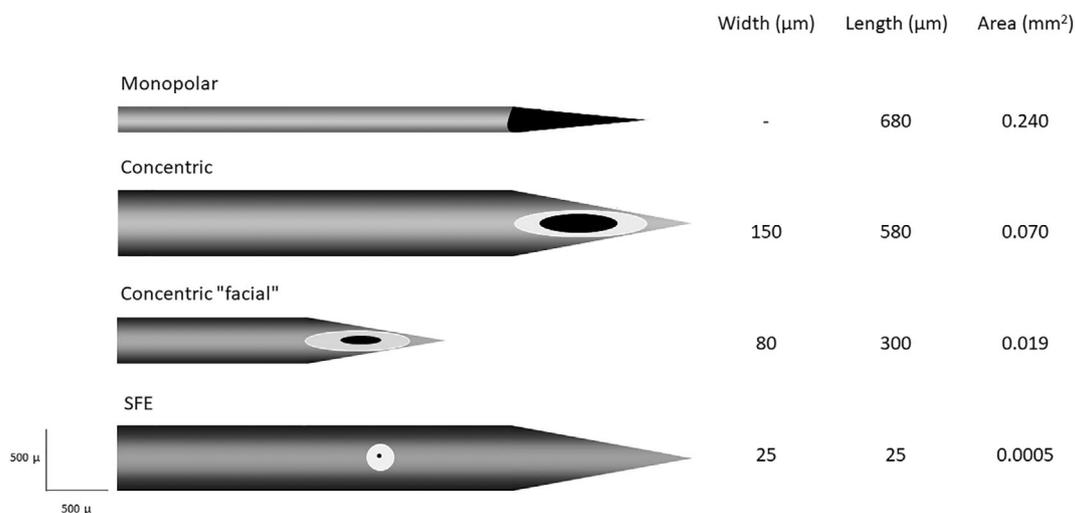


FIGURE 1 Relative size of four different EMG electrodes. Dimensions are listed at the right

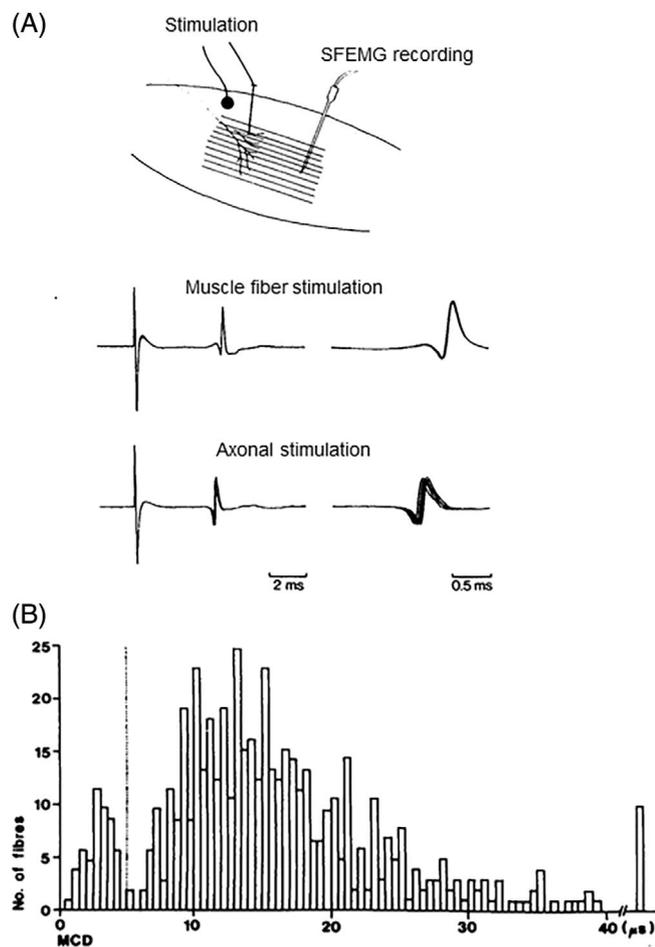


FIGURE 2 SFEMG recording using intramuscular stimulation. A, Stimulating and recording electrodes are shown at the top. Examples of responses to direct muscle fiber stimulation (low jitter, $< 5 \mu\text{s}$) and to axonal stimulation (jitter $\geq 5 \mu\text{s}$) are shown in the middle. B, Distribution of jitter values in the ED with direct ($< 5 \mu\text{s}$) and axonal stimulation ($\geq 5 \mu\text{s}$). The vertical dividing line is drawn at $5 \mu\text{s}$. (modified from Stålberg, Trontelj, and Sanders¹ with permission). SFEMG, single fiber electromyography

activation of the tested muscle, when there is a tremor, in children who are too young to cooperate, in unconscious patients, or when it is desirable to control the firing rate precisely, as when assessing the effect of firing rate on jitter. The motor axon can be stimulated proximal to its entry into the muscle, or individual motor axons or their branches may be stimulated within the muscle. The former technique is ideal for facial muscles since branches of the facial nerve can be stimulated percutaneously or with a monopolar needle electrode proximal to the entry of the nerve into the muscle (Figure 3A). For limb muscles, intramuscular axonal stimulation is performed with a monopolar needle electrode inserted near the motor endplate zone (Figure 3B). Another needle electrode or surface electrode is used as the anode for stimulation.

Stimulation is delivered with a stimulus duration of 0.1 ms at 2–10 Hz, and the stimulus intensity is adjusted to produce a slight twitch of the muscle. The SFE is inserted into the twitching portion of the muscle and positioned to record clearly defined single-fiber action potentials

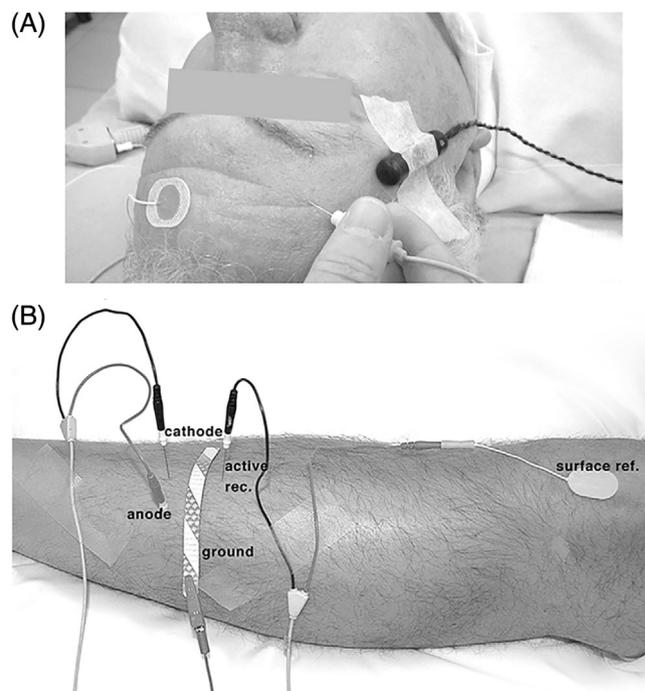


FIGURE 3 Stimulation activation with a surface electrode (A) and intramuscular monopolar needle electrode (B). Rec, recording; ref, reference.

(SFAPs). As the stimulus intensity is increased, increasing numbers of SFAPs are elicited. When the stimulating needle is optimally placed near a nerve branch, stimulation can be achieved with very low-intensity pulses, activating only a few motor axons. Care must be taken to assure that stimulation is supramaximal for each motor axon; liminal stimulation produces variable latency and impulse blocking that is indistinguishable from abnormal neuromuscular jitter and blocking. When further increasing the stimulus intensity no longer decreases the jitter (1–3 mA is usually sufficient), the jitter can be confidently measured between the stimulus and the SFAPs (Figure 4). The multiplex detection method for latency measurement allows simultaneous analysis of many spikes in multispike recordings. Since all spikes occur synchronously in such recordings, it is also possible to detect and quantify concomitant jitter, which often arises at the stimulation point. Unlike voluntary activation, motor axon stimulation does not follow the Henneman size principle, i.e., motor units are not activated in order of their size.

It should be noted that increasing the stimulus intensity to overcome liminal stimulation may activate neighboring axons, which in turn are subliminally stimulated. Experience and careful technique are necessary to avoid misinterpretation when increased jitter is seen during axonal stimulation. (The authors recommend that the technique of voluntary jitter measurement be mastered before relying on stimulation jitter studies for diagnosis.)

Jitter can be measured in all clear, distinct SFAPs at each recording site, provided they satisfy testing for supraliminal stimulation. To approximate physiologic activation rates, activation at 10 Hz is usually used when calculating jitter. The recording electrode is moved to several different sites within each tested muscle to minimize the

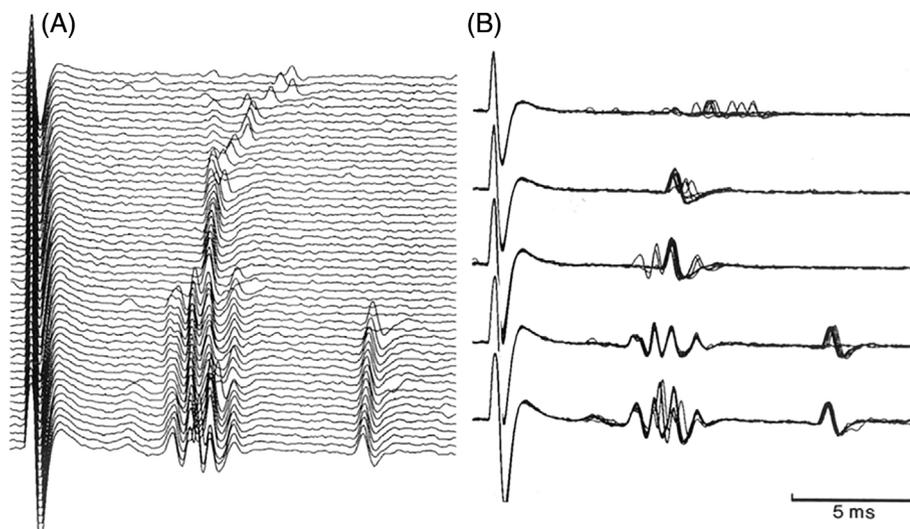


FIGURE 4 Recordings for jitter measurement during axonal stimulation. Initial tall spike is the stimulus artefact. A, Rastered signals. Only one spike with large jitter is activated initially. With increasing stimulation intensity (from top to bottom), the jitter of the first spike decreases and additional spikes are recruited, some of which initially have long latency and large jitter. B, The spike shapes are best seen when the signals are superimposed. (from Stålberg, Trontelj, and Sanders¹ with permission)

possibility of recording signals more than once from the same muscle fiber. For an optimal sampling of each muscle during axonal stimulation, signals should be measured from at least 30 endplates before reporting a conclusion for the tested muscle. With nerve stimulation, the jitter represents time variability in just one motor end-plate for each spike. SFAPs elicited by nerve stimulation have jitter 5 μ s or greater, whereas jitter is less than 5 μ s when the muscle fiber is stimulated directly.

1.4 | Jitter measurement during voluntary activation

Measuring jitter during voluntary activation of the muscle requires greater patient cooperation than stimulation activation but has fewer technical problems that can lead to misinterpretation of the results. As the patient slightly contracts the muscle, the recording electrode is inserted into the muscle and positioned to record two or more time-locked APs from the same motor unit (Figure 5). The electrode position is adjusted to assure that all signals of interest have a rise time of less than 300 μ s and an amplitude greater than 200 μ V. Signals are acquired by triggering on one spike, and the neuromuscular jitter is seen as variations in the position of the non-triggering spike(s) (Figure 5B,C). The jitter in each pair of signals represents the combined jitter in the endplates of the triggering and non-triggering spike. To adequately sample a muscle, jitter should be measured from 100 (a minimum of 50) discharges of 20 potential pairs recorded from different muscle parts, using two to four skin insertions.

1.5 | Analysis of jitter

Jitter is expressed as the mean value of consecutive differences (MCD) of successive interpotential intervals (IPIs), calculated from the following formula:

$$MCD = |IPI_1 - IPI_2| + |IPI_2 - IPI_3| + \dots + |IPI_{n-1} - IPI_n| / n - 1$$
 where IPI_i is the interpotential interval. When stimulation activation is used, the IPI is represented by the stimulus–response latency. The normal mean MCD varies among different muscles. In most muscles with disturbed NMT, the jitter is normal in some endplates and increased in affected endplates (Figure 6A,B); with more pronounced disturbances, individual muscle fibers fail to respond to nerve activation, producing neuromuscular blocking (Figure 6C).

The IPI in a given muscle fiber is influenced by the length of the preceding interdischarge interval (IDI), the so-called “velocity recovery function” (VRF),³ which may introduce additional IPI variability due to differences in the effect of VRF among different muscle fibers. This can be avoided during stimulation activation jitter studies by using a constant stimulus rate and excluding from the jitter calculation the data in the initial second of each train or after the operator changes the stimulation rate. It should be noted that even if the activation rate is constant, intermittent impulse blocking will produce variable IPIs in the blocked muscle fibers, and the resulting VRF effect will contribute additional jitter (Figure 7). The effect of variable firing rates during voluntary activation jitter studies can be minimized by sorting the IPIs according to the duration of the preceding IDI, then calculating the mean of the consecutive IPI differences in the new sequence; the result is called the mean sorted-data difference (MSD). When there are large variations in the firing rate, the MSD is lower than the MCD and should be used as the jitter value. If there are trends in the IPI values, the MCD will be less than the MSD and should be used as the jitter value. Some EMG equipment calculates the MCD and MSD and can automatically use the smaller values as the jitter value.

To assure that acceptable signals are being acquired, feedback is provided to the operator in different ways during data acquisition. Some systems electronically store and redisplay the waveforms for review. The operator can then exclude unacceptable waveforms before final calculations are made.

For jitter measurements, a signal acquisition threshold voltage level is set automatically or by the operator to select spikes of

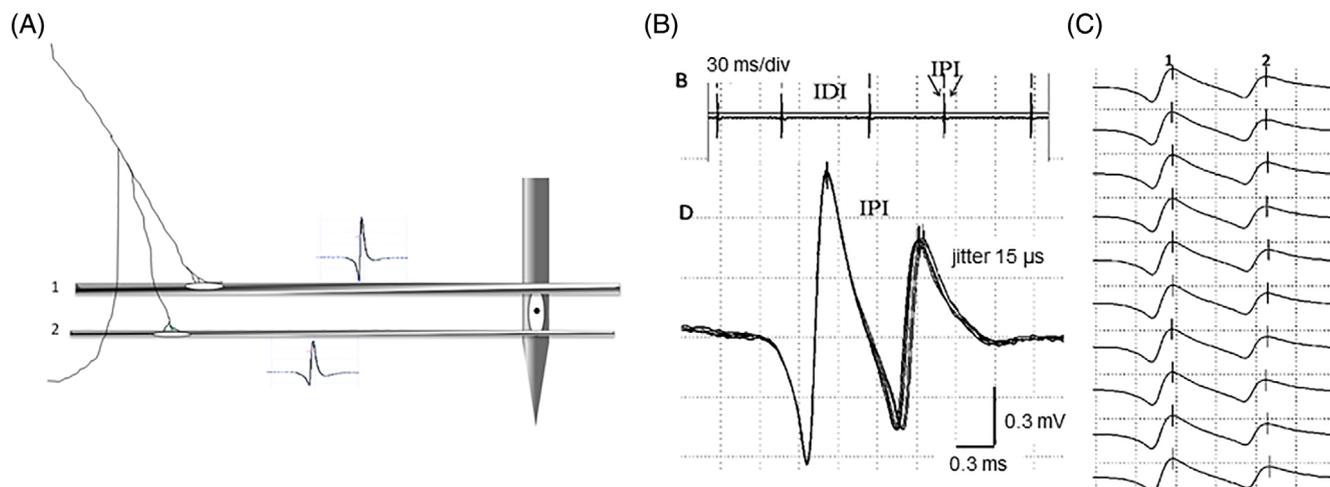


FIGURE 5 Recordings for jitter measurement during voluntary activation. The SFE is positioned to record from a pair of muscle fibers innervated by the same motor axon. A, The action potential pair firing with slight voluntary effort, with the IDI and IPI indicated. B, Several superimposed discharges demonstrate changes in the IPI (the neuromuscular jitter). C, Rastered display of the two potentials in B at a higher sweep speed. The sweep is triggered by the first potential. (modified from Stålberg, Trontelj, and Sanders¹ with permission)

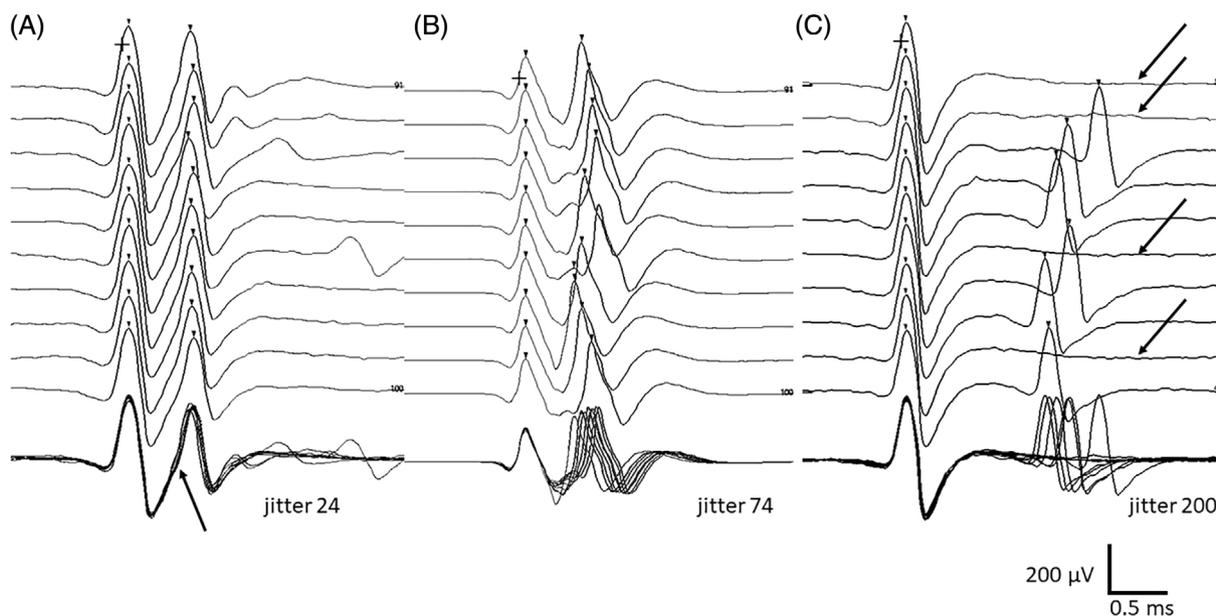


FIGURE 6 Jitter during voluntary activation using concentric needle electrodes. A, Normal jitter. B, Increased jitter. C, Increased jitter with intermittent impulse blocking (arrows). The rising phase of the second spike in (A) seems to have an inflection (arrow), but this is the shape when the second component of the spike arises from a sloping baseline

interest and exclude undesired signals. Interval values may be measured between points on the spikes where the voltage passes an operator-determined level, the so-called “voltage level technique” (Figure 8A). Some systems employ an algorithm to automatically identify all peaks of the spikes that fulfill acceptance criteria and calculate interval values between the peak of the triggering spike and these peaks, the “multipeak detection technique” (Figure 8B). This technique is more accurate than the voltage level technique in signals that are riding on each other, which is not uncommon in concentric needle electrode (CNE) recordings (Figures 8C and

11F). The IPI values can be displayed graphically, which permits visualization of the distribution of data and any trends (Figure 9). Such displays also make it easier to detect extreme values that do not follow the expected data distribution. It should be emphasized that no system can reliably distinguish true blocking from spurious signals; the operator must make this determination based on examination of the signals and enter this information into the record.

Recordings with long IPIs may have erroneously elevated jitter values due to the VRF effect, particularly if the firing rate is irregular.

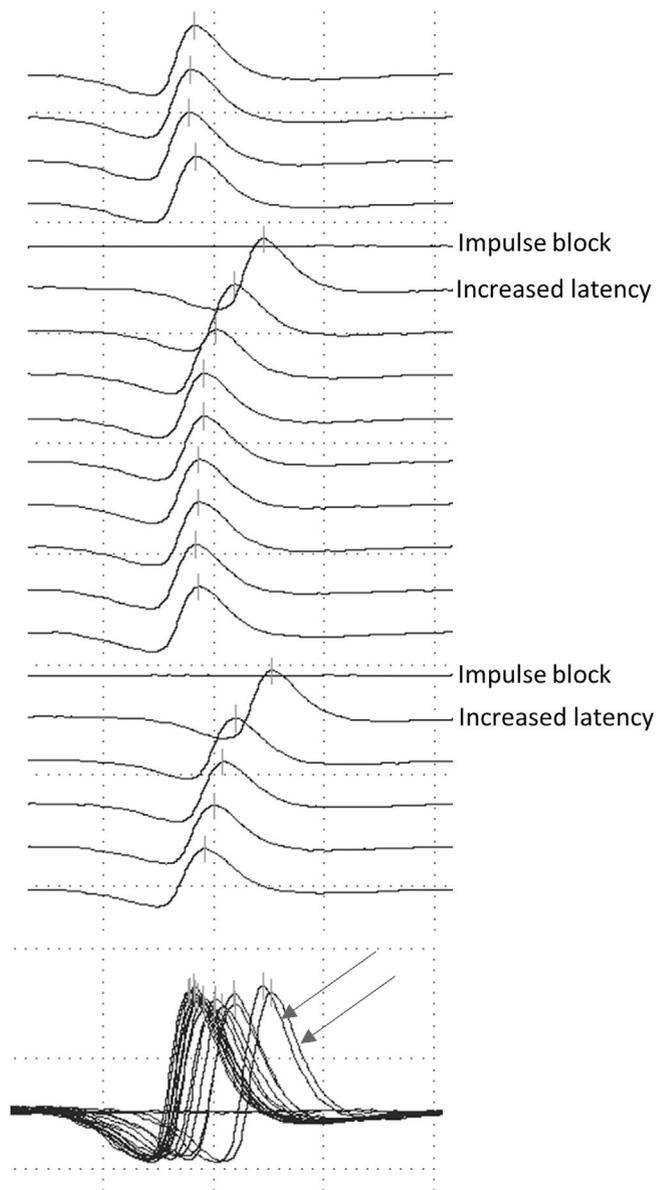


FIGURE 7 Effect of the VRF after impulse blocking during stimulation activation. Signals are rastered (above) and superimposed (bottom). Note the increased latency (arrows) due to slowed conduction in the responses following each impulse block, the VRF effect

Thus, published reference values are valid only for IPIs less than 4 ms. The MSD calculation, as described above, reduces but does not entirely compensate for the effects of muscle fiber conduction velocity variations induced by the VRF effect.

The mean MCD may exceed normal limits when only a few individual jitter values are extremely high. Such high jitter values are usually accompanied by intermittent blocking, which gives irregular activation that adds jitter because of the VRF effect. To accommodate this, jitter values greater than $150\ \mu\text{s}$ should be truncated to $150\ \mu\text{s}$ for calculating mean values. Median values of MCD may also be used to express the central tendency of the data, and truncated values are also used here.

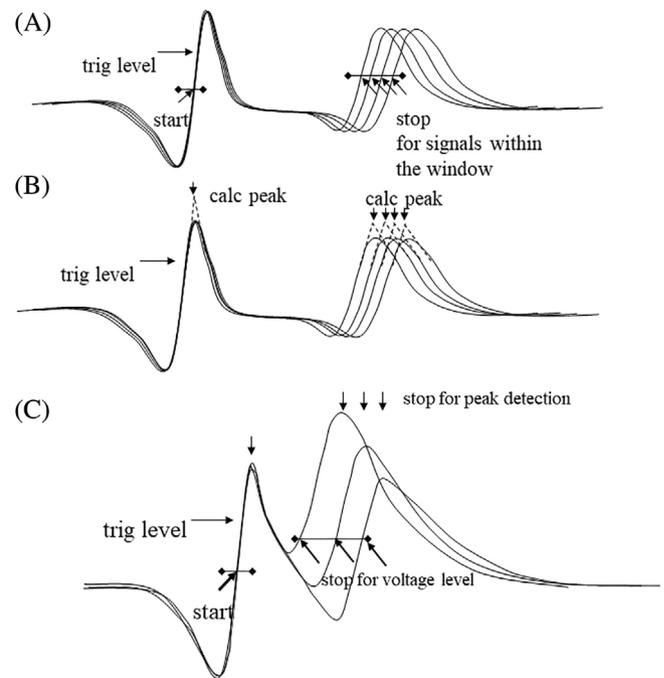


FIGURE 8 Different methods for measuring IPIs. A, Voltage level technique. B, Multi-peak detection technique. For well-separated signals, both methods give the same results. C, When the second spike is riding on the falling phase of the first, the voltage level method gives erroneous results and should not be used

It is helpful to present the results of jitter measurements in each muscle graphically, along with the mean (and sometimes also the median) value of the MCD values from all the pairs or endplates that were measured, the percentage of paired potentials or endplates in which blocking was seen (percent with blocking), and the percentage of pairs or endplates in which jitter exceeded the normal limit for that muscle (percent abnormal pairs or endplates).

A study is abnormal if the mean (or median) jitter exceeds the upper limit for the muscle or if more than 2 out of 20 voluntary-activated pairs or 3 out of 30 stimulation-activated peaks have increased jitter. Jitter less than $5\ \mu\text{s}$ is rarely seen in voluntary-activated jitter studies in normal muscles and is found in myopathies. The low values probably result from APs produced by both branches of a split fiber,⁴ which are activated by a single neuromuscular junction (NMJ).⁵ These low values should not be included in the assessment of NMT.

MCD values measured during stimulation activation are less than those measured during voluntary activation of the same muscle because they come from single endplates. Reference values for jitter during stimulation activation have been determined for the extensor digitorum (ED) and orbicularis oculi (OO) muscles.^{6,7} For other muscles, normative values for stimulation studies can be obtained by multiplying the voluntary jitter reference values by a conversion factor of (0.71). MCD values less than $5\ \mu\text{s}$ obtained during electrical activation result from direct muscle fiber stimulation and should not be included in the jitter calculation.

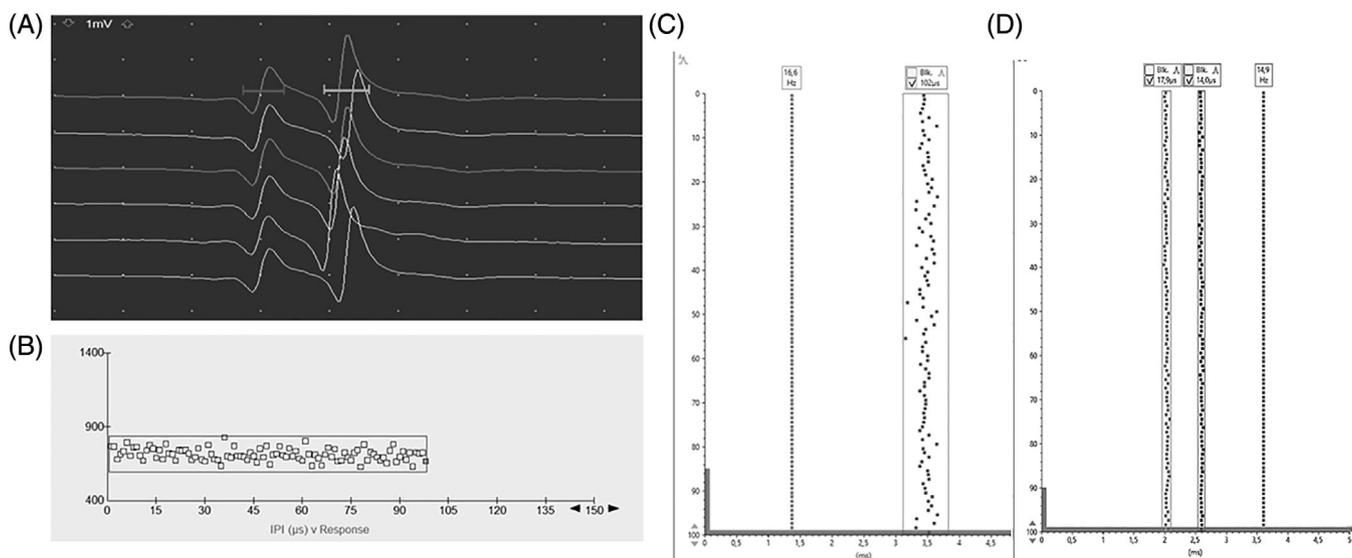


FIGURE 9 Different displays of consecutive interspike intervals. A, Signal in raster mode. B, Sequential plot of interspike intervals from signal (A), time on X-axis. C, Same data as (B), time on Y-axis. D, Sequential plot of interspike intervals in a triple potential, time on Y-axis

1.6 | Technical considerations

The electrodiagnostic consultant must have considerable experience with SFEMG to perform adequate jitter studies. Many EMG machines incorporate automated jitter analysis techniques that significantly reduce analysis time. Most adult patients can cooperate for adequate SFEMG studies. Patient discomfort rarely limits the use of this test, even when two or more muscles must be examined. If the patient has a tremor, it may be impossible to make adequate recordings from distal muscles during voluntary activation. In this case, recordings can be made from facial or more proximal arm muscles, or stimulation activation can be used. Children over 8 y of age can usually cooperate well enough for adequate SFEMG studies. In uncooperative children, jitter studies can be performed with axonal stimulation.⁴

Jitter measurement cannot be entirely automated by any system since the electrodiagnostic consultant selects the signal to be analyzed and determines the quality. Selection of the recording position of the electrode and the epoch to analyze have more effect on the jitter results than does the equipment. There is more variation among the results obtained by different operators using the same equipment than one operator using different equipment. Even so, inter-operator differences should be minor when standard techniques are used, as demonstrated in a multicenter project to obtain reference values.²

2 | MEASURING JITTER WITH CNES

Due to restrictions on using re-sterilized material, the SFE has been replaced by the smallest CNE, customarily called a facial needle. This is now the most commonly used electrode for jitter analysis.

2.1 | Recording principle

Because of the larger recording surfaces in even the smallest CNE compared to SFEs (Figure 1), it is difficult to determine if spikes recorded with these electrodes are produced by single muscle fiber APs or by summation of APs from 2 or more muscle fibers. By increasing the low-frequency (high-pass) filter settings, it is possible, to some extent, to identify SFAPs within motor unit action potentials recorded with a CNE (Figure 10). Acceptable spikes recorded with a CNE have been referred to as “apparent single-fiber action potentials” (ASFAPs).^{8,9} Because the higher high-pass filter setting reduces the amplitude of recorded signals, spikes as low as 50 μ V are accepted for CNE jitter measurement if they have a rise time less than 300 μ s.

Because of their larger pickup area, monopolar needle electrodes are even more likely to record summated APs and should not be used for jitter analysis. Fiber density measurements can only be made with SFEs.

2.2 | Reference values for jitter

A multicenter collaborative study determined reference jitter and FD values for SFE recordings for many muscles (Table 1).^{2,10} These jitter reference values are valid only for interspike intervals up to 4 ms; recordings with longer interspike intervals may have erroneously high jitter values, particularly if the firing rate is irregular. Using the MSD calculation, as described above, does not entirely compensate for the effects of muscle fiber conduction velocity variations in recordings with long interspike intervals, especially if there are also slow trends in the intervals.

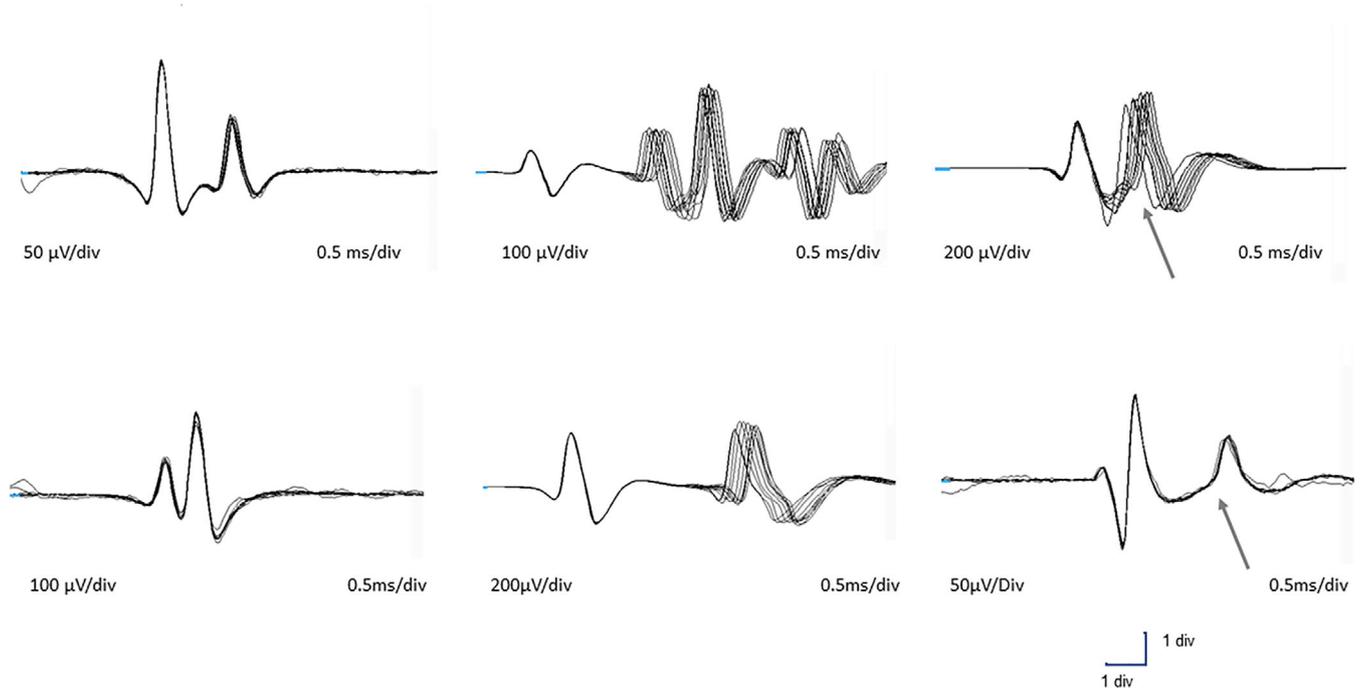


FIGURE 10 CNE recordings with acceptable sharply-rising spikes having parallel rising phases without notches or shoulders. Signals with arrows are acceptable since the shoulders on these signals (arrows) are due to origination of the second spike component on the sloping falling phase of the first component

Electrode	OO		Frontalis		ED	
	CNE ¹⁰	SFE	CNE ¹⁰	SFE	CNE ¹⁰	SFE
Voluntary activation						
Mean MCD	31	40 ^{2a}	28	34 ^{2a}	30	35 ^{2a}
Individual jitter	45	55 ^{2a}	38	51 ^{2a}	43	50 ^{2a}
Stimulation activation						
Mean MCD	27	20 ⁶	21	23 ^{11,12}	24	25 ⁷
Individual jitter	36	30 ⁶	28	35 ^{11,12}	35	40 ⁷

TABLE 1 Reference jitter values (μs) for SFEs and CNEs

^aAge = 30 y.

In some muscles, there is a slight increase in jitter with age. This may be caused by denervation/reinnervation changes with age and is more prominent in distal muscles.

A study is abnormal if either of the following criteria is met:

- The mean jitter exceeds the upper limit for the muscle, or
- Jitter is increased in more than 2 of 20 pairs (voluntary activation) or 3 of 30 endplates (stimulation activation).

In most studies, the conclusions from both criteria are concordant. Occasionally, the mean MCD is increased in myasthenia gravis (MG) when fewer than 2 out of 20 potential pairs have increased jitter; the converse is uncommon.

2.3 | Reference values for CNE jitter

Reference values have been published for jitter measured with a CNE during voluntary activation for ED,^{13,14} OO,^{13,14} and frontalis muscles,¹⁵ as well as during stimulation activation for these muscles.¹⁶⁻¹⁸

Reference values for jitter obtained with a CNE are about 5 μs lower than those obtained with an SFE.⁹

A multicenter study to establish reference values for jitter measurements in the ED and frontalis muscles using a CNE was published in 2012.¹⁹ However, the high-pass filter settings used in this study were 2 kHz, higher than had been previously recommended, the electrode size and jitter measurement algorithm were not standardized,

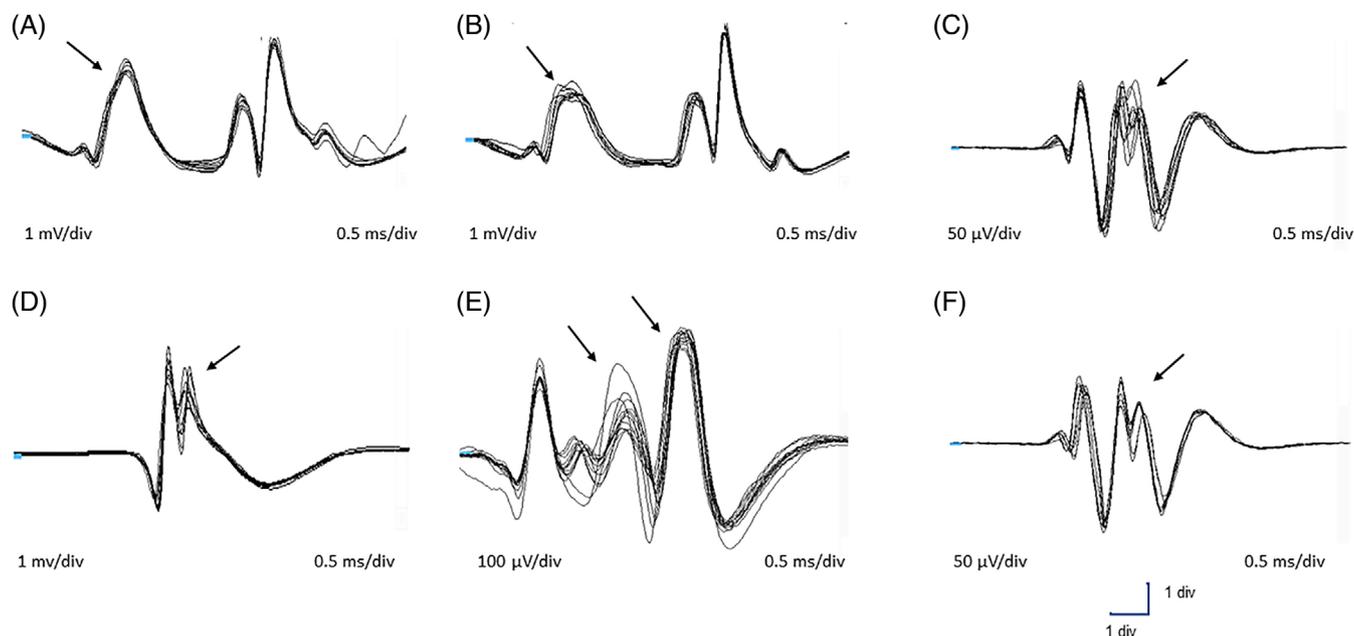


FIGURE 11 Concentric needle electrode recordings. A-E, Arrows indicate unacceptable signals. A, Shoulder on rising phase. B, Blunt spike. C, Irregular shape of the middle complex indicates summation of two spikes this signal is also seen in (F), where triggering is on the second spike, which now gives an acceptable recording. D, Variable spike amplitude. E, Variable shape of the third component and a blunt peak of the last spike

and the obtained values were larger than in reported studies in which the peak-detection algorithm was used.^{14,16–18} If these reference values are used, the diagnostic sensitivity will be reduced, and abnormal jitter would not be detected in many MG patients, especially in those with mild disease.

A multicenter, multinational project to obtain CNE reference jitter values for voluntary and stimulation activation jitter using the criteria listed below was published in 2016 (Table 1).¹⁰ It should be emphasized that these reference values are only valid for studies performed using an electrode with a recording area of 0.019 mm², a high-pass filter of 1 kHz, and a low-pass filter of 10 kHz (or an alternative low-pass filter of 3 kHz, see under section 2.4) and the following signal quality criteria:

- The spike amplitudes should be greater than 50 μ V and constant in consecutive discharges, although slight variation can be accepted (Figure 10).
- The rising phase of the spikes should be parallel in the superimposed display (Figure 10).
- Spikes with a notch or “shoulder” should be excluded as these are produced by more than one AP. The interaction of the comprised APs unpredictably influences jitter measured from such spikes (Figure 11).
- Jitter should be measured only between spikes separated by a clear baseline if a voltage algorithm is used. If a peak-detection algorithm is used, jitter can be measured between clearly defined spikes even if there is no baseline between them, but the time between negative peaks should be $>150 \mu$ s.

2.4 | Quality control

The operator should exert quality control at several points during the process to help assure that the data obtained are valid:

- **During signal acquisition:** The spikes should be sharp and noise-free (high-frequency noise can be reduced by changing the high frequency [low-pass] filter from 10 kHz to 3 kHz, which causes no significant loss in AP shape) and meet the selection criteria for ASFAPs. The trigger point should be on a stable portion of the potential. The population of motor units in the muscle must be appropriately sampled. Blocking should be noted during signal acquisition.
- **During analysis:** The filmed or recorded signals should meet the acceptance criteria, and the trigger point should be stable. Spurious triggering signals should be recognized and excluded. Blocking should be verified and noted.
- **During data presentation:** The IPIs from a pair of potentials should be distributed without a multimodal pattern (Figure 12). The results should fit the subjective impression formed during signal acquisition.
- **During interpretation of the data:** The interpretation should make sense considering the clinical information. If not, the data should be questioned.

Guidelines for jitter measurements with SFEs and CNEs were published in 2019.²⁰

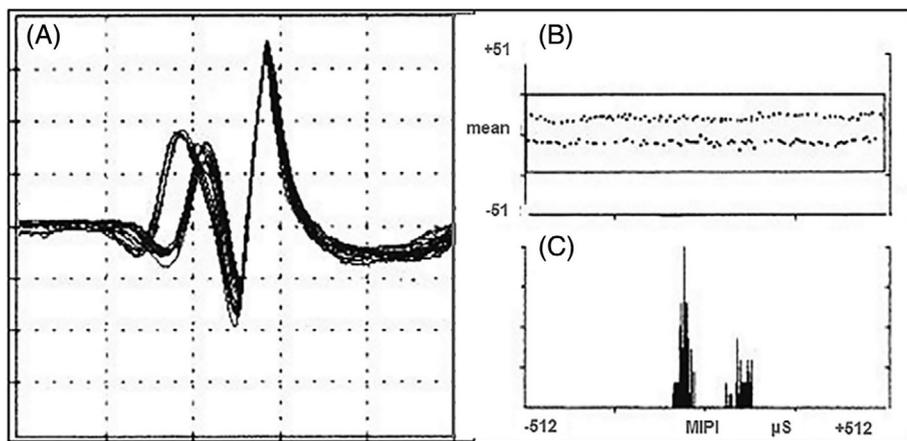


FIGURE 12 Dual latency distribution, a so-called “flip-flop.” A, superimposed signals, triggered on the last spike. B, sequential plot of IPIs, demonstrating dual latencies. C, Non-sequential histogram of IPIs, demonstrating bimodal distribution. The underlying cause is unknown. Do not measure jitter in such a recording or, if possible, use only one of the two latencies. MIPI, mean IPI

3 | PITFALLS IN JITTER RECORDINGS

The following are pitfalls encountered when measuring jitter with SFEs.

3.1 | During voluntary activation

- Too much muscle activity, which is a common occurrence, limits the ability to obtain good signal quality. Instruct the patient to activate less and use the EMG sound as guidance.
- An unstable triggering point can add instability to the entire recording if the amplitude level method is used. This may be caused by a fluctuating baseline, electrode movement, or triggering on more than one signal.
- Firing rate-dependent jitter due to the VRF effect may increase jitter values measured as the MCD. This is largely compensated for by calculating the MSD.

3.2 | During stimulation activation

- Excessively intense stimulation can cause multispike recordings. Spikes from multiple motor units superimpose and interfere with each other. To avoid this, use short stimulus pulses of less intensity.
- Liminal stimulation gives rise to spike latency variation, adding to that already generated in the NMJ. To avoid this, begin with a weak stimulus and increase the stimulus intensity until only a few spikes are obtained and measure only the spikes in which the jitter is not further reduced with further increased intensity. When increasing the stimulus intensity, it is imperative to follow only the selected spike(s) since the relative stimulus intensity varies among the fibers seen on the screen.
- The effect of the VRF will give rise to artefactually increased jitter if jitter is measured during the initial second after stimulation begins or after the stimulation rate is changed (Figure 13). Do not measure signals during these times.

- The so-called “axon reflex,” a less common pitfall, is seen with intramuscular needle stimulation. The muscle fiber is alternatively stimulated indirectly via an axonal branch or directly via its terminal twig (Figure 14).²¹ When the two routes for stimulation of the same muscle fiber produce a clearly bimodal distribution, the phenomenon is easily detected. Sometimes, however, the minimal latency variation (Figure 14C) passes undetected, and the calculated jitter is artefactually increased.

3.2.1 | Pitfalls in CNE recordings

In general, CNE recordings are prone to the same pitfalls as those with SFEs. Due to less selective recording, interference between spikes from different motor units is more pronounced, making CNE recordings more complex and challenging to quantify appropriately, especially during stimulation activation.

4 | MEASURING JITTER IN CHILDREN

Children greater than 8 y old can usually cooperate during voluntary activation jitter studies; in younger children, stimulation activation can be used. A technique called stimulated potential analysis using concentric needle electrodes (SPACE) relies mainly on the visual assessment of spike variability in multispike recordings.^{22,23} The reported sensitivity to detect neuromuscular dysfunction is 84%, the positive predictive value is 36%, the negative predictive value is 96%, and specificity is 71%.²⁴ The SPACE technique is seen as a screening test for jitter abnormalities in children. Reference values specific to the SPACE technique must be used.

5 | JITTER IN MG

SFEMG demonstrates increased jitter in virtually all patients with MG, even in muscles with normal strength.²⁵ No one muscle is more

FIGURE 13 VRF effect at the beginning of stimulation trains with different stimulation rates. There is a several second pause between trains. Note the latency shortening at the beginning of each train, particularly at the higher stimulation frequencies. (modified from Stålberg, Trontelj, and Sanders²¹ with permission)

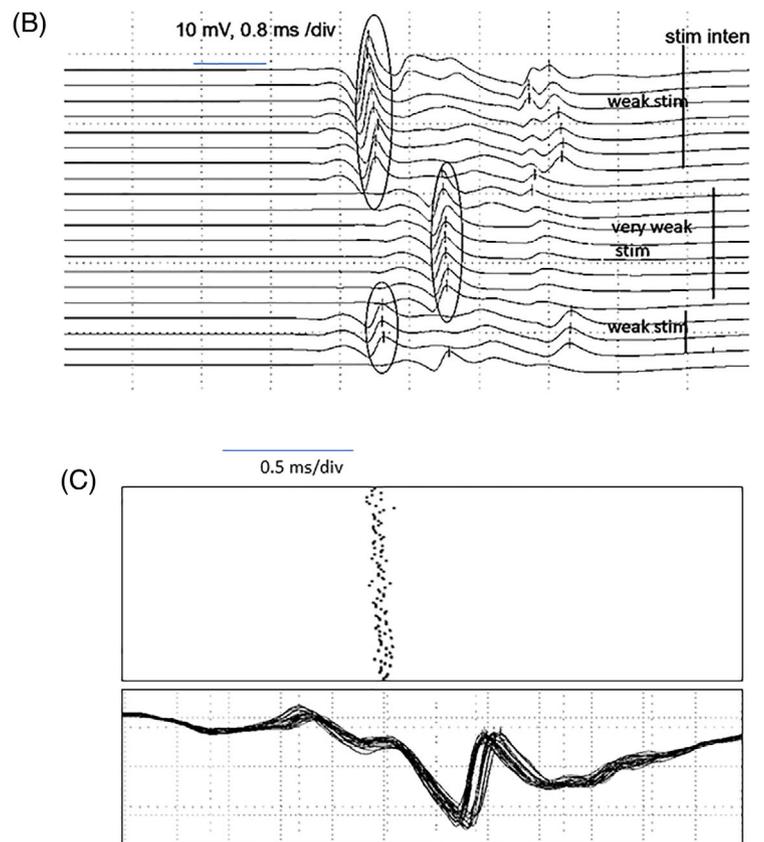
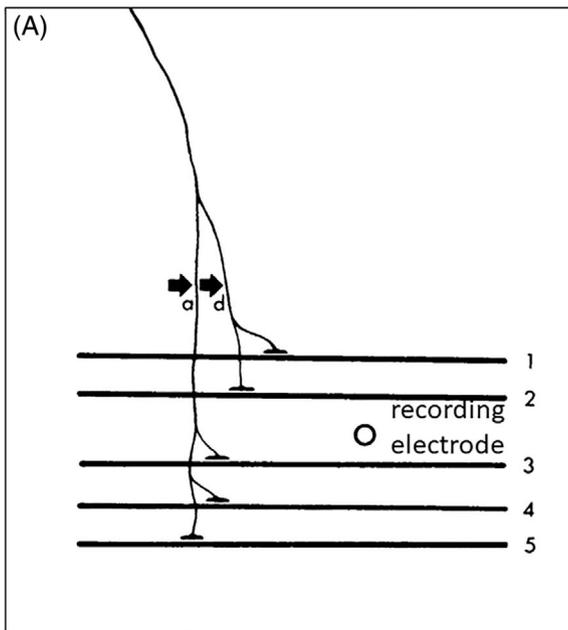
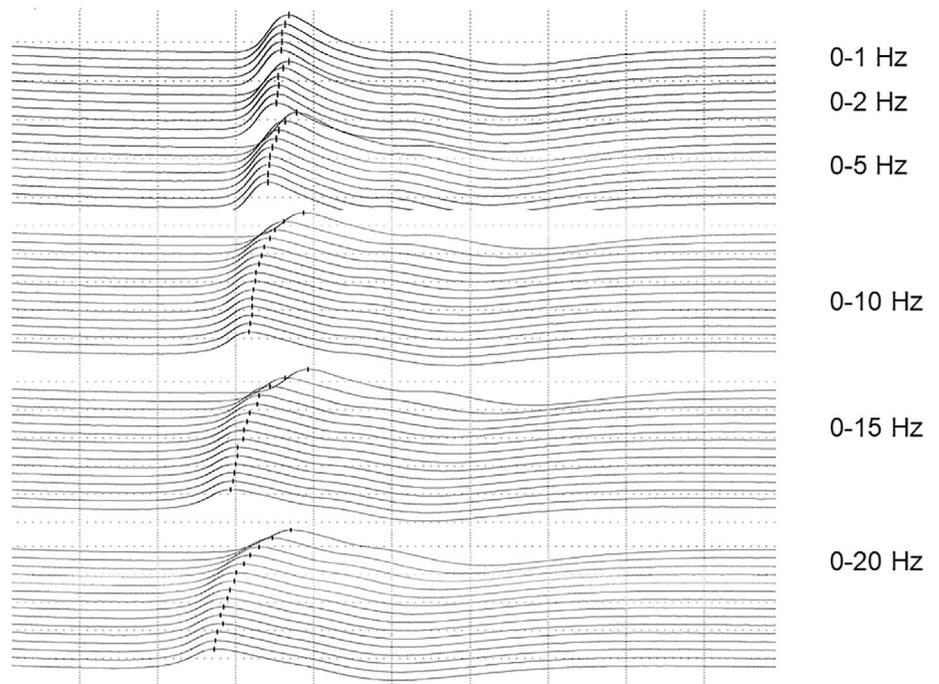


FIGURE 14 The so-called “axon reflex.” A, Two routes of activation (arrows): Weak stimulation (A) produces retrograde activation to the proximal branch point, then activation of the terminal twig to the motor unit. D, Stronger stimulation activates the terminal nerve twig to the motor unit directly. B, This results in dual latencies. C, Small latency differences may be difficult to detect, and recordings may be falsely considered to have large jitter

abnormal in every patient with MG, and the muscle(s) to be tested should be selected based on the patient's symptoms. A facial muscle usually is examined first, either the frontalis or OO. If jitter is normal in this muscle, then the other facial muscle should be tested, or if any limb muscle is weak, jitter should be tested in that muscle. The distribution of abnormal jitter differs in some patients with antibodies to muscle-specific tyrosine kinase (MuSK) (see below). If jitter is normal in a muscle with definite weakness, the weakness is not due to MG.

Abnormal jitter is found in a limb muscle in more than half the patients with ocular myasthenia, demonstrating that the physiologic abnormality is more widespread than the clinical findings suggest in these patients.²⁶

In some MG patients with anti-MuSK antibodies (MMG), weakness and jitter abnormalities are distributed in a pattern different from other myasthenic patients.²⁷ For example, in MMG patients with predominant facial and pharyngeal muscle weakness, jitter may be normal in the ED but markedly abnormal in facial muscles. Likewise, in MMG patients with weakness predominantly in neck or shoulder muscle, jitter may be normal in both the ED and the facial muscles. In these patients, examination of a weak neck or a shoulder muscle may be necessary to demonstrate abnormal jitter.²⁸

5.1 | Sensitivity/specificity of jitter testing

The sensitivity of jitter studies in MG performed with either CNEs or SFES using either voluntary or stimulation activation is virtually identical.²⁰

To obtain the maximum sensitivity of jitter testing, it must be recognized that no one muscle is abnormal in all patients with MG and that patients with more severe disease are more likely to have abnormal jitter in any given muscle. The ED is abnormal in up to 100% of patients with severe generalized MG and most patients with purely ocular muscle involvement.²⁵ Overall, jitter is increased more often in facial muscles, either the OO or frontalis²⁵; however, extensive studies comparing the sensitivity in these two muscles are not available. The maximum sensitivity of jitter testing is obtained if a symptomatic weak muscle is examined.

Although increased jitter is highly specific for abnormal NMT, abnormal NMT itself is not specific for any one condition, being a feature of many neuropathic and some myopathic conditions. Thus, the specificity of increased jitter for MG in any given population will depend on the proportion of patients in that population who have any of these conditions. In assessing a muscle for MG, care must be taken to assure that the muscle is free of nerve or muscle disease and that the patient has not recently received botulinum neurotoxin (BoNT) (see the Jitter after BoNT section below). In an early study, jitter was increased in either the ED or frontalis in 85% of MG patients, and when both of these muscles were normal, testing a third muscle (OO) showed increased jitter in almost all patients.²⁹

5.2 | Serial jitter studies

Repeat jitter studies are a sensitive measure of change in MG disease severity.^{26,30,31} A study comparing the change in jitter with clinical change in MG concluded that all jitter parameters (absolute and % change in MCD, % pairs with normal jitter, and % pairs with blocking) correlated with and predicted clinical change.³¹ Measurement of jitter has been recommended as the most robust biomarker of NMT for clinical trials.³²

5.3 | Jitter after BoNT

BoNT is used therapeutically in patients with spasticity, blepharospasm, hemifacial spasm, cervical dystonia, focal dystonia, hyperhidrosis, hypersalivation, pain relief as in migraine, and in other conditions when muscle relaxation is needed. Pharmacologically, the toxin causes a presynaptic blockade with inhibition of release of acetylcholine, but clinically its effect is mainly due to denervation.

In addition to its effect on injected muscles, BoNT also spreads throughout the body and produces increased jitter in muscles distant from the injection site.³³ The effect of therapeutic BoNT is long-lasting, often persisting to some degree for 6 mo or more,³⁴ and no exact time can be determined for its complete disappearance. The long-lasting effect is usually greatest in muscles close to the injected muscles and probably is not dose-dependent for the neighboring or distant muscles.

A previous BoNT injection in a patient with myasthenia-like symptoms has considerable practical consequences. It is not uncommon for such patients to be referred for jitter studies to exclude MG. If increased jitter is detected in contrast to the clinical impression, ask if the patient has had a previous BoNT injection. In a recent study of 78 patients receiving BoNT for movement disorders, jitter was abnormal in a neighboring muscle in 40% and in a distant muscle in 14%.³⁴ The study authors suggest that jitter studies in the ED could be helpful clinically 8 mo after a previous BoNT injection in the face or neck and after 11 mo in a neighboring facial muscle if a higher upper limit of mean MCD in the tested muscle is used.

6 | JITTER IN LAMBERT–EATON MYASTHENIC SYNDROME

Jitter is markedly increased in Lambert–Eaton myasthenic syndrome (LEMS), frequently out of proportion to the severity of weakness, with frequent impulse blocking. This results from the pathophysiology of NMT in LEMS, which is somewhat different from that in MG.³⁵ In addition to fluctuations of the endplate threshold, the jitter may also reflect variability of the slope of the endplate potentials that reach threshold, in which case there may be increased jitter but no blocking. There is a characteristic effect of firing rate in many endplates in LEMS, the jitter and blocking decreasing as the firing rate

increases.^{36,37} However, this pattern is not pathognomonic for LEMS since jitter and blocking may also decrease at higher firing rates in some endplates in patients with MG.

7 | JITTER IN CONGENITAL MYASTHENIA

Congenital myasthenic syndrome (CMS) or congenital myasthenia is a large group of rare hereditary illnesses due to defects in proteins that make up the NMJ, leading to a compromised safety margin of NMT.³⁸ These defects can be presynaptic, synaptic, or postsynaptic, and there are no particular jitter findings in most forms that distinguish them from other NMJ disorders. Molecular studies are required to make a specific diagnosis in most cases and will not be discussed here.

Weakness usually manifests in infancy or childhood, although some forms of CMS can initially manifest in teenagers and adults. Distinguishing CMS from MG and other neuromuscular illnesses such as chronic progressive external ophthalmoplegia (CPEO) can sometimes be challenging. CMS is often responsive to specific symptomatic treatment, and thus this distinction is crucial in clinical practice.

The reported sensitivity of repetitive nerve stimulation (RNS) in CMS ranges from 65 to 88%,^{39–41} and jitter sensitivity ranges from 85 to 93%, depending on the CMS form.^{22,41–43} CMS should be suspected in all patients with fluctuating weakness, abnormal decrement on RNS, or increased jitter when antibodies for MG are not present and there is no response to immunotherapy.

8 | SFEMG FINDINGS IN NEUROGENIC DISORDERS

Reinnervation of denervated muscle fibers takes place by collateral sprouting of intramuscular nerve fibers and regeneration from the end of transected nerve fibers. Collateral sprouting produces remodeling of the motor unit and increased numbers of muscle fibers per motor unit. On muscle biopsy, this is seen as fiber-type grouping and increased terminal innervation ratio. With SFEMG, this is seen as increased FD and jitter. Jitter is increased within days after nerve injury,⁴⁴ and FD may be increased 3–4 wk after nerve injury, before reinnervation changes are seen on muscle biopsy or conventional needle EMG studies. Jitter is increased during the reinnervating process, regardless of the cause. As reinnervation becomes established and FD increases, the jitter becomes less. This implies that NMT is uncertain or impaired in immature synapses. This is also reflected by an abnormal decrement on RNS, which is common in amyotrophic lateral sclerosis.⁴⁵

In a recent study of 32 patients with chronic radiculopathy, jitter was increased with stimulation or voluntary activation in all cases when the muscle showed fibrillation potentials and positive waves.⁴⁶ Conversely, when the muscles showed chronic neurogenic motor unit action potentials without active denervation, jitter was increased in 79% of the muscles studied with voluntary activation and in 68% with stimulation activation. These findings

highlight the importance of not misinterpreting increased jitter as MG in muscles with active denervation or chronic reinnervation. This is particularly important when the studied muscle is prone to radiculopathy (e.g., the ED in C7 radiculopathy).

SFEMG can help demonstrate or exclude abnormalities in patients with mild or questionable neuronal disease. In peripheral neuropathies, more distal muscles have the most marked abnormalities. A more patchy distribution is seen in diseases such as syringomyelia or motor neuron disease. By testing multiple muscles, the distribution of abnormality can be demonstrated, even when mild or subclinical. The combination of jitter and FD can also provide information about the stage and completeness of reinnervation, increased FD with stable motor unit potentials (MUPs) indicating that reinnervation is complete. Most neuropathies are progressive, however, and increased jitter and blocking in these conditions may be seen at all stages due to simultaneously ongoing denervation and reinnervation. In MUP analysis, increased jitter of contributing muscle fibers is seen as shape variability (“jiggle”) of the MUP on consecutive discharges.⁴⁷

9 | SFEMG FINDINGS IN MYOPATHY

SFEMG demonstrates abnormalities in muscle disease that may not be apparent by other electromyographic techniques. Although these findings may not be specific to a particular disease, they frequently increase our understanding of the disease process by demonstrating the presence of abnormal NMT or re-arrangement of muscle fibers within the motor unit. This information complements the findings from more conventional needle EMG examinations. FD is increased in some muscle diseases but tends to be much less in myopathies than in neuropathies in muscles with a similar weakness. The increased FD in myopathies suggests focal fiber-type grouping in some areas and probably loss of fibers in other parts of the MU territory. The focal increase in FD can be due to muscle fiber splitting, innervation of regenerated muscle fibers, packing of muscle fibers due to atrophy, or ephaptic recruitment of muscle fibers. Jitter is also increased in some myopathies, possibly due to uncertain conduction in immature motor axons, transmission across immature or degenerating motor endplates, and threshold ephaptic transmission.

Jitter may be increased in some myopathies, such as CPEO, and may resemble MG, although it is usually not difficult to distinguish between these conditions.⁴⁸ It should be emphasized that in CPEO, the jitter is slightly increased without blocking, and no decrement is found on RNS.⁴³ In MG, jitter is usually greater in facial muscles, whereas most myopathies other than CPEO spare these muscles.

It should be emphasized that although individual SFEMG findings are not specific for any disease, the relative degree of abnormality of individual parameters, the distribution of abnormalities among different muscles, and their combination frequently assist in making the correct diagnosis when evaluated in the context of the clinical picture and the results of other diagnostic information.

10 | EFFECT OF DRUGS

In practical terms, most drugs do not increase jitter, other than those active at the NMJ (e.g., curariform agents, acetylcholinesterase inhibitors). However, jitter was slightly increased in the ED in patients taking calcium channel blockers, such as verapamil and amlodipine.⁴⁹ Jitter is usually increased in patients with MG even if they are taking cholinesterase inhibitors. Exceptionally, jitter may be normal in patients with mild MG taking pyridostigmine and is increased when discontinued.⁵⁰ Based on these observations, the authors do not recommend routinely withholding cholinesterase inhibitors before jitter testing. However, if jitter is normal in a patient taking these medications, it is recommended that the studies be repeated at least 12 h after they are discontinued if it is safe to do so.⁵¹

11 | OTHER USES OF SFEMG

SFEMG and filtered CNE signals can be used for precise latency measurements other than for assessing NMT. Examples include H⁵² and blink reflex⁵³ studies and measuring conduction velocity in individual motor axons.⁵⁴

These signals can also be used as a marker to trigger independent events. One example is the spike-triggered averaging of surface recordings in motor unit number estimate techniques where signals from SFEMGs, CNEs, or monopolar electrodes may be used.⁵⁵ It should be mentioned that sometimes conventional CNE recordings are preferred as a marker since the shape of SFAPs does not reveal if they are generated by fibers from different motor units.

ETHICAL APPROVAL

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

CONFLICTS OF INTEREST

Drs. Sanders and Stålberg receive royalties for the book "Single Fiber EMG." Dr. Kouyoumdjian has nothing to disclose. This paper underwent peer review by the AANEM Monograph Review and Development Committee and review by the Muscle & Nerve editor, but did not undergo additional, external peer review. AANEM monographs are designed to be broadly educational to AANEM members and others with interests in neuromuscular, musculoskeletal, and electrodiagnostic medicine, and may at times be outside of the narrower scope of other articles published in Muscle & Nerve.

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