Defining Normal Duration for Afterdischarges With Repetitive Nerve Stimulation: A Pilot Study

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Abstract: The presence of afterdischarges on repetitive nerve stimulation may be useful to diagnose cramp fasciculation syndrome, however, the presence and normal duration of afterdischarges has not been well-defined in the normal population and individuals with other neuromuscular diseases. The aim of this pilot study was to describe the distribution of afterdischarge durations in normal controls and patients with peripheral neuropathy. The estimated seventy-fifth percentiles of the afterdischarge durations following tibial nerve repetitive nerve stimulation at 2, 5, 10, and 20 Hz were 315, 688, 745, and 928 milliseconds for 18 normal patients, and 143, 31, 323, and 542 milliseconds for 18 peripheral neuropathy patients respectively. Afterdischarge durations were similar in peripheral neuropathy patients and controls. These findings suggest that afterdischarge durations of more than 500 milliseconds are common in normal controls without subjective cramps and patients with peripheral neuropathy, with some durations beyond 1,000 milliseconds. Therefore, the presence of afterdischarges on repetitive nerve stimulation should be interpreted with caution when evaluating patients for hyperexcitable nerve syndromes.

Key Words: Cramp fasciculation syndrome, Repetitive nerve stimulation, Peripheral nerve hyperexcitability, Peripheral neuropathy, Afterdischarges.

(*J Clin Neurophysiol* 2009;26: 45–49)

Peripheral nerve hyperexcitability is used to describe a number of syndromes that clinically manifest with muscle cramps, stiffness, fasciculations, and/or myokymia. The involuntary motor unit activity is felt to be related to hyperexcitability of the motor nerve or the nerve terminal (Auger, 1994; Layzer, 1994). These syndromes include acquired neuromyotonia ("Isaac syndrome"), rippling muscle disease, and "cramp-fasciculation syndrome" (CFS). Peripheral nerve hyperexcitability syndromes have historically has been diagnosed clinically and supported by electrodiagnostic findings, such as the presence of myokymic or neuromyotonic discharges on needle electromyogram (EMG). However, in CFS, myokymic and neuromyotonic discharges may not be present, making a definitive diagnosis more difficult. In addition to the needle examination findings, in disorders of peripheral nerve hyperexcitability, abnormalities of the nerve membrane, often due to abnormalities of the potassium channel, may lead to repetitive or sustained firing of an induced action potential along the nerve that may persist following cessation of a stimulus. These "afterdischarges" or occasionally true sustained cramp discharges have been shown to occur following repetitive nerve stimulation (RNS) at various rates following cessation of the repetitive stimulus in peripheral nerve hyperexcitability syndromes (Harrison and Benatar, 2007).

Patients with muscle stiffness, pain, or cramps are a common referral for electrodiagnostic studies and a "cramp fasciculation study" protocol utilizing repetitive stimulation studies at various frequencies is often performed as part of the evaluation of these patients to attempt to identify disorders of peripheral nerve hyperexcitability. The presence and duration of afterdischarges reflects the presence and degree of hyperexcitability of the nerve membrane, with longer duration afterdischarges suggesting a larger degree of hyperexcitability. Although the presence of afterdischarges supports a peripheral nerve hyperexcitability syndrome, the diagnostic utility is limited. First, the presence and duration of afterdischarges in the normal population has not been well defined. As a result, the significance of a brief afterdischarge (e.g., one lasting 200–500 milliseconds) that occurs in an individual patient is unclear. Second, afterdischarges are also present in other neuromuscular diseases (Tahmoush et al., 1991; Verdru et al., 2002). Third, the determination of whether an afterdischarge is truly involuntary in a patient is inexact and, in some cases, voluntary contraction of the muscle being stimulated due to pain or poor relaxation may resemble an involuntary discharge.

The aim of this study was to determine the distributions of afterdischarge durations among normal individuals and patients with peripheral neuropathy (PN) for the tibial nerve using four different frequencies of repetitive stimulation: 2, 5, 10, and 20 Hz. It was hypothesized that normal individuals and patients with PN will frequently experience afterdischarges.

MATERIALS AND METHODS

Subjects

The study was approved by the Institutional Review Board. All patients referred to the Mayo Clinic EMG laboratory for the evaluation of symptoms of PN or muscle cramps were considered for enrollment. Patients referred for arm -symptoms who met eligibility criteria defined below and normal volunteers from the community were recruited for the control group. All subjects enrolled in the study provided informed signed consent. Subjects were classified as having PN or as normal controls according to clinical and routine electromyographic features (not including the RNS protocol). All patients completed a questionnaire related to the presence and frequency of cramps, including the site of cramps, and cramp severity on a visual-analog pain scale.

All patients underwent routine nerve conduction studies (NCS) and needle EMG performed according to standard laboratory technique and protocol as indicated for their referring complaint

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The authors report no conflicts of interest.

Accepted for Presentation at the American Association of Neuromuscular and Electrodiagnostic Medicine annual meeting, October 2007, Phoenix, AZ.

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ISSN: 0736-0258/09/2601-0045

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(Daube, 2002). In addition to the routine EMG, patients referred for arm symptoms without a history of leg symptoms underwent a routine tibial motor nerve conduction study including tibial F-wave responses and a sural sensory NCS to exclude subclinical peripheral nerve disease.

Inclusion criteria for normal controls included no history of leg pain, numbness, or weakness, no history of a lumbar radiculopathy, a normal neuromuscular examination, normal tibial motor and sural sensory NCS, and no subjective history of cramps. Patients were excluded from being a normal control if they had any abnormal findings on their clinical examination, an abnormality of any parameter of the tibial motor or sural sensory NCS, a history of a generalized neuromuscular disorder or focal neurologic process involving the legs, previous lumbar spine surgery, a history of defined focal trauma to the foot, ankle or leg, or neurologic symptoms in the legs including subjective history of leg cramps in the past 6 months.

The inclusion criteria for PN included symptoms of PN, including bilateral foot numbness or tingling, neurologic examination findings of reduced or absent Achilles reflexes, symmetrical distal foot or leg sensory loss or weakness, and abnormal NCS in at least one nerve in the lower extremity. Both demyelinating and axonal peripheral neuropathies were included. Patients were excluded if there was an absent tibial motor response (to exclude severe involvement of the tibial nerve in which the CFS protocol could not be performed), or clinical or EMG findings of other neuromuscular disorders.

Twenty normal controls and 20 PN patients were recruited, although for reasons detailed in the Results section the final sample sizes were 18 in each group. In addition, a small reference sample of 6 CFS patients was studied.

Cramp Fasciculation Study Protocol

The CFS protocol was performed on the tibial nerve recording over the abductor hallucis and stimulating the tibial nerve at the ankle. The compound muscle action potential was recorded with 5 mm disc electrodes taped to the surface of the skin over the abductor hallucis muscle 1 cm inferior to and 1 cm posterior to the navicular tubercle. A reference electrode was placed over the medial aspect of the first metatarsal-phalangeal joint. The nerve was stimulated using a bipolar surface stimulator electrode held over the tibial nerve at the ankle, approximately 8 cm proximal to the recording electrode. The recording setup consisted of a free-run sweep of 500 milliseconds per division for a total recording sweep of 5 seconds with a gain of 200 uV/division.

Three baseline recordings of 10 seconds each with no stimulation were first obtained to define the number of fasciculations at rest and the amount of voluntary motor unit potentials that may be present from poor relaxation. When motor unit potentials were firing at rest, methods to ensure appropriate relaxation were used, including passive manipulation of the toes or verbal encouragement for relaxation. Patients were also instructed to try to remain relaxed during and after the stimulation. Slow trans of 0.5 Hz stimuli were administered with gradually increasing stimulus intensity to ensure a supramaximal response. Once a supramaximal compound muscle action potential was obtained, a train of four stimuli at a frequency of 2 Hz was administered. Only four stimuli were given to minimize the degree of pain and voluntary contraction the muscle, which may occur with a higher number of stimuli. The four stimuli were repeated at frequencies of 5, 10, and 20 Hz with a minimum of 60 seconds between the end of each afterdischarge and the next set of 4 stimuli. Patient relaxation before each set of stimuli was assessed by visual and auditory recognition of the recorded potentials.

The primary parameter evaluated was the duration of the afterdischarge. An afterdischarge was defined as the continuous, high frequency motor unit potential firing that occurred without a pause, immediately following the shock artifact. The duration was defined as the distance from the shock artifact from the fourth stimulus in the train to the end of the afterdischarge. Afterdischarge duration was quantified by two methods. First three examiners blinded to the clinical status of the subjects subjectively determined the duration of post-RNS afterdischarge duration by marking that point on the wave form tracings where surface-recorded abnormal motor activity ceased, in the opinion of the examiner for the first quarter of the patients. Because of a clear lack of examiner agreement on the end of the discharge, two of the same blinded examiners subsequently quantitatively determined afterdischarge durations using the criterion that the end of the afterdischarge was the point where there was a pause of 80 milliseconds or more in the firing of motor unit potential (a return to baseline). This criterion correlates with a decrease in the firing rate of motor unit potentials to less than 13 Hz and would be indicative of the end of the continuous high-frequency firing of motor unit potentials following the stimuli (Fig. 1). Using the defined criterion, two investigators, blinded to the clinical grouping of the patients, independently marked the end of the afterdischarge on separate printouts of the study. Data analysis and conclusions that follow are based on quantitative analysis using the "80 milliseconds pause" rule.

Statistical Methods

Numerical variables were summarized with the sample median, minimum, twenty-fifth and seventy-fifth percentiles, and maximum. These quartile-based summaries were more appropriate than the more commonly used mean and standard deviation because the distributions of many of the variables were heavily skewed. Categorical variables were summarized with number and percentage. The mean of the afterdischarge durations from the two different electromyographers was used for each patient in analysis. No attempt was made to determine particular cut-off values for afterdischarge durations that might discriminate between normal and abnormal due to the small sample sizes. Agreement between electromyographers was summarized as the proportions of patients for whom afterdischarge durations differed by less than 0.5 and 1 second.

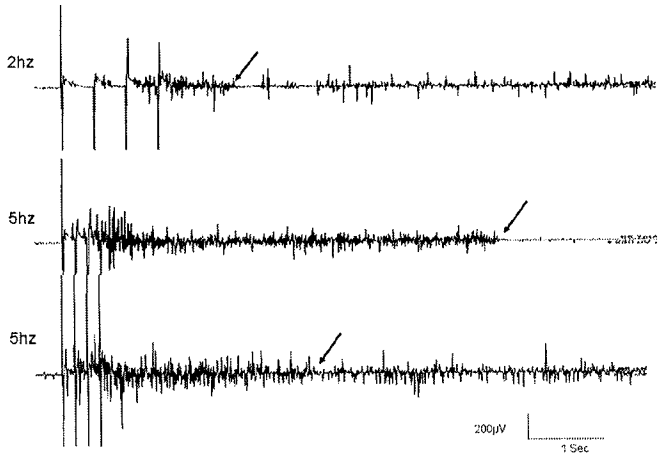

FIGURE 1. Examples of afterdischarges from three different patients demonstrating the end of each afterdischarge (arrows).

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RESULTS

Twenty normal, and 20 PN patients were recruited, however, two patients were later excluded from each group for the following reasons. One "normal" patient was found to have abnormalities on tibial and sural NCS and therefore was excluded. Another normal patient had persistent baseline activity before the electrical stimulation making it difficult for the observers to determine the end of the discharge and therefore this patient was excluded as well. Two patients in the PN group demonstrated obvious volitional movement immediately after the administered stimuli, and the persistent motor unit activity ceased immediately after the patients relaxed. Since these were not true afterdischarges, these patients were excluded.

Table 1 shows patient demographics, including the frequency of cramps and fasciculations. All but 2 (89%) of the PN patients experienced cramps. Most patients (64%) who experienced cramps rated the severity at 7 or higher on the pain scale. Table 2 summarizes afterdischarge durations in the PN and control patients; the seventh-fifth percentile of the afterdischarge durations for controls at 2, 5, 10, and 20 Hz were 315, 688, 745, and 928 milliseconds, respectively. Figure 2 shows afterdischarge durations according to group at all four frequencies. This figure additionally includes the afterdischarge durations of six CFS patients for reference. As expected, these tended to be higher than for normal and PN patients, although there was more overlap than expected. One normal control experienced a cramp discharge with a clinical cramp at 20 Hz. This patient denied a history of cramps with or without exercise. There was no evidence of any association between afterdischarge duration and frequency of cramps in the PN group (data not shown). Observer agreement in identifying the end of afterdischarges is summarized in Table 3.

TABLE 1. Patient Demographics, Cramp Frequency, and Fasciculations

Variable	Normal (n = 18)	Peripheral Neuropathy (n = 18)
Age[a]	44 (30, 36, 52, 83)	69 (34, 59, 75, 85)
Gender		
Male	7 (39%)	13 (72%)
Female	11 (61%)	5 (28%)
Frequency of cramps		
Never/rarely	17 (100%)	2 (11%)
Less than once per month	0 (0%)	4 (22%)
Once per month	0 (0%)	3 (17%)
Once per week	0 (0%)	5 (28%)
Once per day	0 (0%)	4 (22%)
Multiple per day	0 (0%)	0 (0%)
No. fasciculations recorded from AH in 30 seconds[a]	5 (0, 0, 10, 88)	5 (0, 1, 15, 144)

[a]Numerical variables summarized with median (minimum, twenty-fifth percentile, seventy-fifth percentile, maximum).

TABLE 2. Duration of Afterdischarge by RNS Frequency

	Afterdischarge Duration (milliseconds)	
Frequency (Hz)	Normal (n = 18)	Peripheral Neuropathy (n = 18)
2	0 (0, 0, 315, 2356)	0 (0, 0, 143, 365)
5	136 (0, 0, 688, 3524)	0 (0, 0, 31, 803)
10	323 (0, 0, 745, 7673)	10 (0, 0, 323, 1001)
20	292 (0, 0, 928, 7965)	94 (0, 0, 542, 12135)

Median (minimum, twenty-fifth percentile, seventy-fifth percentile, maximum) is shown.

RNS, nrepetitive nerve stimulation.

DISCUSSION

Peripheral nerve hyperexcitability syndromes, such as "cramp fasciculation syndrome" are clinically defined disorders that present with muscle stiffness or cramps. While the presence of myokymic and neuromyotonic discharges on EMG or the presence of voltage-gated potassium channel antibodies in the serum are helpful to confirm disorders such as Isaac syndrome or "rippling muscle disease," these findings are typically absent in CFS and the diagnosis is suspected purely on a clinical basis. Since muscle cramps are a common clinical problem often referred to the EMG laboratory for evaluation, it would be useful to have a technique that can help to distinguish patients with occasional cramps from those due to disorders such as CFS. Repetitive nerve stimulation studies assessing the presence and degree of persistent motor unit potential activity ("afterdischarges") may be helpful in the diagnoses of peripheral nerve hyperexcitability syndromes, such as "cramp fasciculation syndrome." The presence and duration of afterdischarges may reflect the degree of persistent firing of an induced action potential along the nerve membrane. Therefore, in patients with CFS due to hyperexcitability of the nerve membrane, RNS may produce afterdischarges or cramp discharges at various stimulation rates (Auger, 1994; Harrison and Benatar, 2007). The duration of the afterdischarges could potentially reflect the degree of hyperexcitability of the nerve.

Benatar et al., recently performed a retrospective study reviewing the presence and frequency of afterdischarges at stimulation rates of 1, 2, and 5 Hz in patients with clinical features of CFS and compared them to those found in other neuromuscular diseases and controls (Benatar et al., 2004). In this study, they used a qualitative assessment of only the presence or absence of afterdischarges or cramp discharges, rather than assessing the duration of the discharges. They reported an 83% sensitivity of a positive study using all stimulation frequencies, but a specificity of only 58%. However, when using only the presence of afterdischarges at 1 Hz stimulation rates, the reported sensitivity was 66% and specificity 76%. While this group used a total of a 1 second train of stimuli at various stimulation rates, longer trains of high frequency nerve stimulation commonly induce cramps in the normal population. As a result, we elected to use brief trains of four stimuli at various rates to assess for hyperexcitability of the nerve that typically would be less likely to occur in normal individuals.

In our experience, many patients seem to show some persistent motor unit potential activity following RNS and it is often difficult to interpret whether a brief persistent discharge is considered a "true" afterdischarge, as demonstrated by the lack of examiners agreement with subjective criterion. The normal range for RNS afterdischarges in normal subjects is not established, limiting the interpretation of the RNS studies in diagnosing CFS (Auger, 1994; Verdru et al., 2002). In our study, the duration of afterdischarges was assessed in groups of normal patients and patients with PN. It was hypothesized that brief duration of afterdischarges would occur in the normal population and patients with PN.

Prolonged afterdischarges or cramp discharges, for example of greater than 1 second, were occasionally seen in normal patients and patients with PN. The normal patients tended to be younger than the PN; therefore some of the differences between groups could have been contributed by age differences. Further investigation with a larger number of CFS patients for comparison may help to clarify

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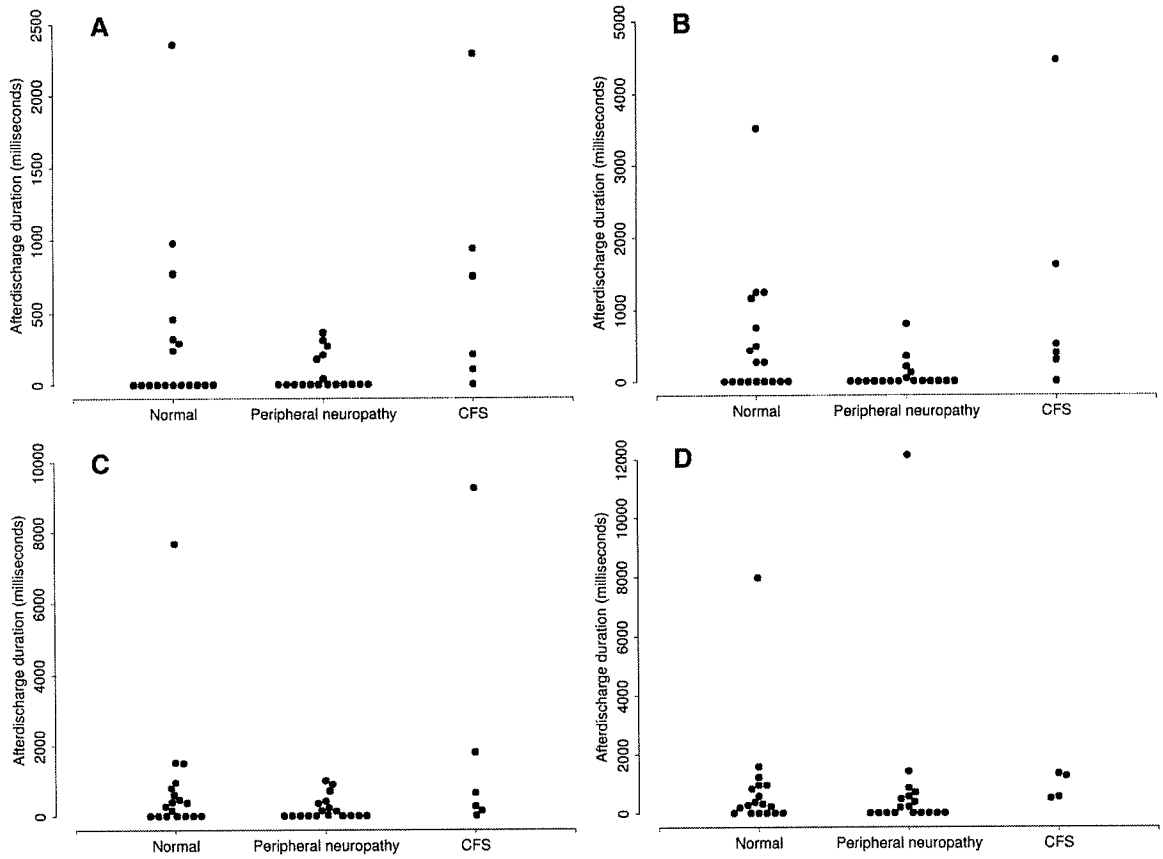

FIGURE 2. Afterdischarge durations at 2 (A), 5 (B), 10 (C), and 20 Hz (D).

TABLE 3. Agreement Between Examiner's Measurements of Afterdischarge Durations

Frequency (Hz)	No. (%) Measured Afterdischarge Durations Within 500 ms Apart	No. (%) Measured Afterdischarge Durations Within 1000 ms Apart
2	37/42 (88%)	39/42 (93%)
5	38/42 (90%)	39/42 (93%)
10	36/42 (86%)	39/42 (93%)
20	29/39 (74%)	35/39 (90%)

any potential differences between the groups. The findings, however, indicate that brief afterdischarges are common in the normal population, with some beyond 1,000 milliseconds.

In our study, the criterion used to identify the end of an afterdischarge differed from previously a reported criterion (Benatar et al., 2004). Previous studies have identified the duration of an afterdischarge by counting the number of individual potentials not present at baseline that followed the train of stimuli. By this criterion, potentials firing at a low rates with a return to baseline between spikes could be considered part of the afterdischarge, when the activity could actually represent fasciculation potentials or potentials from mild voluntary contraction. We elected to use an objective criterion for the duration of the afterdischarge, defined as only the continuous, high frequency firing of motor unit potentials, to reduce a potential artifactual increase in the duration of the discharge from poor relaxation, fasciculations, or baseline noise. Since single normal voluntary motor unit potentials should not fire at rates of higher that 12 Hz without the recruitment of other motor unit potentials, we used a baseline pause of 80 milliseconds (equivalent of a single potential firing at 13 Hz) to indicate the end of an afterdischarge. By using this strict criterion for denoting the end of the afterdischarges, there is a potential that the actual duration of some discharges is underestimated. However, without the use of strict criterion and with simple "eyeballing" the end of a discharge at the point where the persistent motor unit activity amplitude returns to baseline, we found marked variability among observers. Although not measured, there is most likely within observer variability and variability among patients with repeated RNS. The variability in determining afterdischarges is probably increased in patients with increased baseline activity or irregular, infrequent firing of potentials.

Other parameters of the afterdischarges, such as amplitude or rectified area, were not assessed in this study. The amplitude and area of the discharges may have a role in reflecting the number of axons that are firing repetitively. However, since the amplitude (and therefore area) of the recorded discharges, when recorded using surface electrodes, is dependent on factors such as the distance of the electrodes from the muscle and the amount of subcutaneous tissue, these parameters may be unreliable. Furthermore, the degree of repetitive firing of an axon would be best reflecetd in the duration of the discharge. In addition, in this study, we used a protocol consisting of the administration of four supramaximal stimuli. Therefore, conclusions about the effect of stimulating the nerve with submaximal stimulus intensities or with a higher number of stimuli cannot be made. While it is theoretically possible that submaximal stimuli could potentially reduce the length or degree of afterdischarges in normal controls or patients without hyperexcitable nerve syndromes more than patients with CFS, further study is required.

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The small number of CFS patients in this pilot study preclude any conclusions regarding the utility of the test in differentiating between different diseases and the normal population. However, the data obtained will be useful for the optimal design of studies with larger numbers of patients to further evaluate the distributions of afterdischarge durations in different patient groups as well as to assess diagnostic utility of RNS. The findings in our study suggest that afterdischarge durations of more than 500 milliseconds are common in normal controls without subjective cramps and patients with PN, with some durations beyond 1,000 milliseconds. Since there is considerable overlap in the distributions of afterdischarge durations in patients with clinical CFS, patients with PN and normal patients, the presence of afterdischarges on RNS should be interpreted with caution when evaluating patients for hyperexcitable nerve syndromes, such as CFS.

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