Peroneal F-wave characteristics under submaximal stimulation

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ABSTRACT

PURPOSE: F-wave studies are valuable tools in clinical neurophysiology. F-wave parameter estimation must be based on multiple F-wave traces due to their inherent variability. Repetitive supramaximal stimulation is uncomfortable for many patients. This study tested the hypothesis that submaximally stimulated nerves yield F-wave parameters equivalent to those obtained with supramaximal stimulation. **METHODS:** Thirty-five peroneal nerves from 27 subjects were stimulated both supramaximally and submaximally. CMAP and F-wave responses from the extensor digitorum brevis muscle were recorded and analyzed offline. Automated algorithms were used to determine F-wave parameters. **RESULTS:** Mean, minimum, maximum F-wave latencies, F-wave duration, and chronodispersion showed no statistically significant difference under the two stimulation conditions. F-wave persistence, amplitude, and subject's discomfort level, were lower with statistical significance. The correlation coefficient of submaximal and supramaximal mean F-wave latencies was 0.977 and their intraclass correlation coefficient was 0.976. The bias of the mean latencies was 0.21 ms and the 95% limits of agreement were less than 5% of the mean F-wave latency. **CONCLUSIONS:** F-waves acquired with submaximal stimulation possess characteristics statistically equivalent to those obtained under supramaximal stimulation, as measured by the latency and duration parameters. Persistence and amplitude were lower. Reduction in discomfort level was also achieved.

Search Terms: F-wave, submaximal stimulation, mean latency, persistence, duration, amplitude, peroneal nerve

INTRODUCTION

F-waves are late responses recorded from a muscle following stimulation of its associated motor nerve. Stimulation of the nerve is normally performed at supramaximal intensity. The utility of F-waves has been demonstrated in multiple clinical applications (Fisher, 1998), including detection of lumbosacral radiculopathy (Toyokura, 1997; Weber, 2000; Wells, 2002), dynamic changes associated with lumbar spinal stenosis (Tang, 1988), early detection of axonal (Olney, 1990; Kuwabara, 2000) and demyelinating polyneuropathies (Fraser, 1992), demonstration of therapeutic response of pharmacological agents such as baclofen (Dressnandt, 1995), and monitoring of changes in the motor neuron pool and central nervous system (Panayiotopoulos, 1996; Espiritu, 2003).

F-wave study parameters include mean, minimum, maximum F-wave latencies, chronodispersion, persistence, duration, and F-wave amplitude. Due to the inherent variability in F-wave responses, these parameters must be estimated based on multiple F-wave traces acquired following repetitive stimulation. Mean F-wave latency, the most robust F-wave parameter, requires accumulation of at least ten individual

F-wave latencies or up to twenty stimuli depending upon the persistence (Panayiotopoulos, 1996; Fisher, 1998). Other parameters such as minimum F-wave latency may require even more individual latencies as its estimate is less robust. Prior studies suggested that up to 30 F-wave latencies or 100 stimuli may be needed to reliably estimate several F-wave parameters (Chroni, 1994; Fisher, 1994). The number of stimuli delivered can be especially high for recordings from antigravity antagonist muscles such as extensor digitorum brevis with an inherently low F-wave persistence (defined as fraction of the stimuli yielding F-waves) (Fisher, 1980). However repetitive supramaximal stimulation may be uncomfortable for some patients, limiting their willingness to accept high stimulus counts and, consequently, their acceptance for the procedure. Minimizing discomfort with submaximal stimulation may improve patients' tolerance for the high stimulus counts needed in a detailed F-wave study.

Several prior studies investigated alternative stimulation techniques to elicit F-wave responses. Median nerve F-waves were acquired with submaximal stimulation that was sufficient to elicit a compound muscle action potential (CMAP) with amplitude 10—20% of the supramaximal CMAP response (DiBenedetto, 2003). There were no statistically significant differences for mean and minimum F-wave latency, chronodispersion, and persistence. An earlier study also examined the effect of submaximal stimulation on several median nerve F-wave parameters (Clinchot, 1994). No significant differences were found for mean F-wave latency, F-wave amplitude, and persistence. Similar investigations on other nerves have not been reported. Other acquisition paradigms that may affect F-wave response characteristics include voluntary facilitation (Nakazumi, 1992), increased stimulation frequency (Fierro, 1991; Clinchot, 1994), and collision techniques (Guiloff, 1991). They are not explored in this study.

Peroneal nerve F-waves have been shown to be valuable in various clinical applications (Eisen, 1977; Toyokura, 1999; Weber, 1998; Baba, 2001; Tsur, 2002; Wells, 2002). Because of its relatively low persistence and high discomfort level, alternatives to supramaximal stimulation of peroneal nerves for F-wave analysis are valuable. In this study, we utilized rigorous statistical techniques to examine the feasibility of using submaximal stimulation for acquisition of peroneal F-waves. We tested the hypothesis that no statistically significant difference existed for F-wave latency parameters obtained under submaximal and supramaximal stimulation. We further hypothesized that the subjective discomfort level would decrease with submaximal stimulation.

METHOD

Subject Recruitment

Volunteers between the ages of 22 and 68 with no implantable medical devices participated in the study and were recruited from co-workers and their relatives. Written informed consent was obtained from each subject prior to the study. A board certified neurologist (JTM) performed a screening neurological examination. This examination revealed no evidence of either peripheral or central nervous system dysfunction.

Nerve Conduction Studies

Deep peroneal nerve conduction studies were performed with subjects in supine position. An FDA cleared (K041320) nerve conduction testing system (NC-stat®, NeuroMetrix, Inc. Waltham, MA) was used to perform F-wave acquisition and analysis (Leffler, 2000; Wells, 2002; Rotman 2004; Vinik, 2004; Fisher, 2005). A prefabricated electrode configuration (peroneal biosensor, NeuroMetrix, Inc., Waltham, MA) was used to record CMAP and F-wave responses from the extensor digitorum brevis muscle (Wells, 2002). An integrated temperature probe measured skin temperature near the stimulating electrodes located between the medial and lateral malleoli. Stimulus duration ranged from 100 to 500 microseconds and the intensity ranged between 10 and 100 milliamps. The supramaximal stimulation intensity was defined as the level at which the CMAP amplitude was stable with increasing stimulation and was automatically determined by a computer algorithm. The submaximal stimulation level was the reduced stimulation intensity at the same duration that elicited a CMAP with an amplitude 50% of the supramaximal CMAP amplitude (Kimura, 1984). Sixty (60) stimuli at submaximal stimulation level were applied at 2 millisecond interval and F-wave responses were recorded. The study was repeated with supramaximal stimulation intensity. The order of the submaximal and supramaximal studies was randomized and subjects were blinded to the intensity. Subjects rated discomfort using a 10-cm visual analog scale with 0 designated as no pain and 10 unbearable.

Data Analysis

A computer algorithm was developed to detect A-waves and axon-reflexes (Kong, 2003). These were defined as a collection of waveform segments nearly identical to one another, with similar onset and peak latency, and with occurrence rate of more than 40%. If the region of A-wave activity overlapped the F-wave responses such that F-wave latencies could not be reliably determined, the F-wave set was excluded from further analysis. F-wave onset latency was determined using an automated computer algorithm (Fisher, 2005). Latencies were compensated for skin surface temperature at 0.390ms/^{o}C based on internal reference range study (data on file, based on 289 peroneal nerves). F-wave amplitude was the largest consecutive peak-to-peak amplitude difference within a 11.25ms window following the onset latency. F-wave persistence was the percentage of F-wave traces having one or more F-waves present whose amplitude was at least 0.5% of the corresponding CMAP amplitude. F-wave latency and amplitude parameters were calculated only if ten or more traces had F-wave latencies assigned for the F-wave set. Minimum and maximum F-wave latencies were defined as the 5th and 95th percentiles of the latency distribution respectively. Chronodispersion was the difference between the minimum and maximum F-wave latency. F-wave duration was calculated by taking the median value of all recorded F-wave durations in the set. Individual F-wave duration is the total time span between F-wave latency onset and final return of F-wave to baseline in each trace (Toyokura, 1998; Toyokura, 2002).

Statistical Analysis

Descriptive statistics, mean and standard deviation (stdev), were calculated on changes from submaximal to supramaximal stimulation for F-wave parameters, stimulation intensity, and discomfort level. F-wave parameters included mean, minimum, maximum F-wave latencies; chronodispersion; persistence; duration; and median F-wave amplitude. The changes were defined as submaximal minus supramaximal. The t-test p-values were determined for the hypothesis that the parameters under the two stimulation conditions had the same mean.

Relationship between submaximal and supramaximal mean F-wave latencies was evaluated via Pearson correlation coefficient for association, intraclass correlation coefficient (Rosner, 1995) for reliability, and relative intertrial variation for precision (Kohara, 2000). The relative intertrial variation is the difference between two measurements as a percentage of the average of the two measurements. Bland-Altman analysis was also used to evaluate the bias and limits of agreement for mean F-wave latency (Bland, 1999). This analysis consisted of calculating and plotting differences between sub- and supramaximal mean F-wave latencies against the average of the two mean latencies for each nerve. The mean difference is called the bias and limits of agreement refer to the 95th percentile range of the differences or +/- 1.96 times the standard deviation of these calculations. The limits of agreement quantify the reliability of a measurement as judged against a reference (supramaximal NCS results).

RESULTS

Twenty-seven subjects (16 females) participated in the study. Their ages ranged from 22 to 68 years (mean=37.3; SD=11.4). Peroneal nerves were tested bilaterally in 8 subjects and unilaterally in the others. Stimulus magnitude and discomfort level comparison were based on all 35 nerves. One nerve was excluded from subsequent analysis because of overlap between an A-wave and the F-wave responses under supramaximal stimulation. An additional five nerves had fewer than 10 F-wave latencies (out of 60 traces) and were not included in the latency related analysis (two had fewer than 10 latencies at both sub- and supramaximal levels, the other three had fewer than 10 latencies only at the submaximal level). Latency results for all but three nerves reported in Table 1 were based on at least 20 F-waves at both submaximal and supramaximal levels. For the remaining three nerves, the submaximal latency results were based on 13, 17, and 18 F-waves and their corresponding supramaximal latency results were based on 21, 31, and 25 F-waves, respectively. Because of persistence differences, mean F-wave latency calculation for a typical nerve was based on 35 F-wave latencies with submaximal stimulation and 45 latencies with supramaximal stimulation. The difference between supramaximal and submaximal F-wave count (out of a total of 60 F-wave traces) ranged from –2 to 21 and the median value of the F-wave count differences between supramaximal and submaximal stimulation conditions was 10. The persistence dropped from 65% under supramaximal to 48% under submaximal stimulation condition. A scatter plot of mean F-wave latencies is presented in Figure 1. The Pearson correlation coefficient between the submaximal and supramaximal mean F-wave latencies was 0.977. The corresponding intra-class correlation coefficient (ICC) was 0.976. A Bland-Altman graph of the agreement between the submaximal and supramaximal mean F-wave latencies is provided in Figure 2. The corresponding bias was 0.21 ms and the 95% limit of agreement was [-1.68, 2.10] ms. For a nerve with 50 ms as its true mean F-wave latency, the 95th percentile of possible mean latency discrepancy between the submaximal and supramaximal stimulation results is limited to 4.2%. The 95% confidence interval for the bias was [-0.16, 0.57] ms. The 5th and 95th percentile values of relative intertrial variation (RIV) were –2.2% and 3.5%, respectively. The first 20 F-wave traces for a single nerve under submaximal and supramaximal stimulation are shown in Figure 3. Cumulative distributions of all recorded F-wave latencies for all 35 nerves under submaximal and supramaximal stimulation are shown in Figure 4.

A comparison of the ten study parameters under submaximal and supramaximal stimulation is given in Table 1. The discomfort level reduction was statistically significant, as were the F-wave persistence and F-wave amplitude parameters. No statistically significant differences were found for any of the remaining parameters.

Table 1. F-wave study outcome comparison between submaximal and supramaximal stimulation†.

	Average Results Over All Eligible Nerves: mean (stdev)		(Sub-Supra) Difference mean (stdev)	Paired t-test (P value)
	Submaximal	Supramaximal		
Stimulus Magnitude (mA)	41 (22)	58 (27)	-16.49 (7.06)	<0.001
Discomfort Level	3.13 (1.74)	4.37 (1.93)	-1.24 (0.86)	<0.001
Persistence	0.48 (0.24)	0.65 (0.24)	-0.16 (0.10)	<0.001
Median Amplitude (uV)	126 (70)	177 (101)	-52 (100)	0.009
Mean Latency (ms)	50.45 (4.32)	50.25 (4.40)	0.21 (0.96)	0.258
Minimum Latency (ms)	47.82 (4.22)	47.54 (4.28)	0.29 (1.21)	0.216
Maximum Latency (ms)	53.79 (4.75)	53.86 (4.93)	-0.07 (1.85)	0.848
Chronodispersion (ms)	5.96 (1.96)	6.32 (2.00)	-0.35 (1.85)	0.315
Median Duration (ms)	9.79 (1.86)	9.80 (1.24)	-0.01 (1.38)	0.973

†F-wave latency and amplitude parameters were calculated only if ten or more traces had F-wave latencies assigned for the F-wave set with 60 F-wave traces. Minimum and maximum F-wave latencies were defined as the 5th and 95th percentiles of the latency distribution.

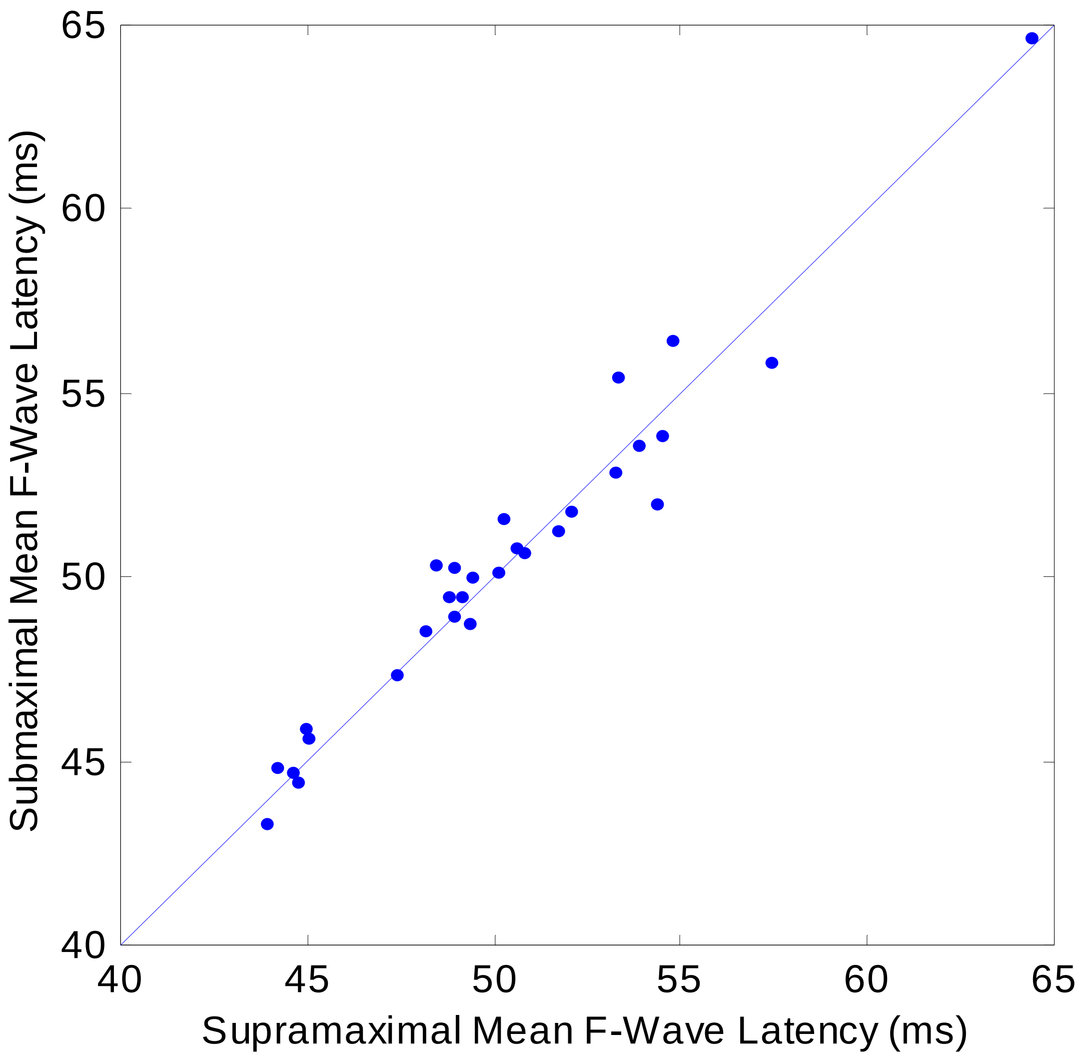

Figure 1. Scatter plot of mean F-wave latencies under supramaximal and submaximal stimulation conditions. Horizontal axis is for mean latencies obtained with supramaximal stimulation and vertical axis is for mean latencies obtained with submaximal stimulation. Pearson correlation coefficient was 0.977, intraclass correlation coefficient has a value of 0.976, and relative inter-trial variation was between –2.2% and 3.5%.

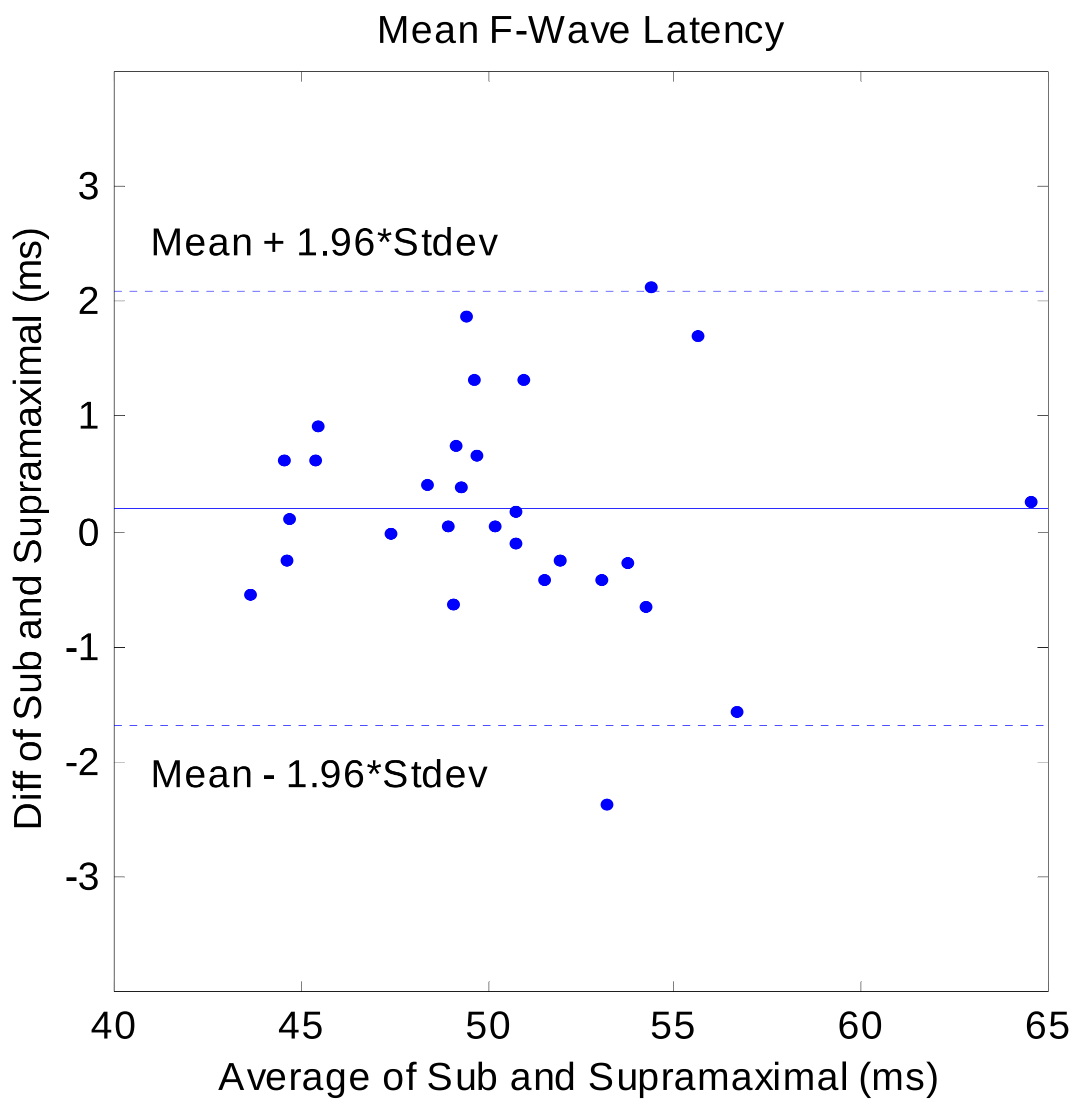

Figure 2. Bland-Altman Plot for assessing the agreement between mean F-wave latencies under submaximal and supramaximal conditions. Horizontal axis is for the average of the two mean F-wave latencies for each nerve and vertical axis is for the difference (submaximal – supramaximal) of the two mean F-wave latencies. The bias, visualized with the solid line, was 0.21ms. The 95% limits of agreement (dotted line) determine the range of possible discrepancies between two mean F-wave latencies. Given a 50 ms true mean F-wave latency, the 95th percentile of possible mean latency discrepancy is limited to 4.2%.

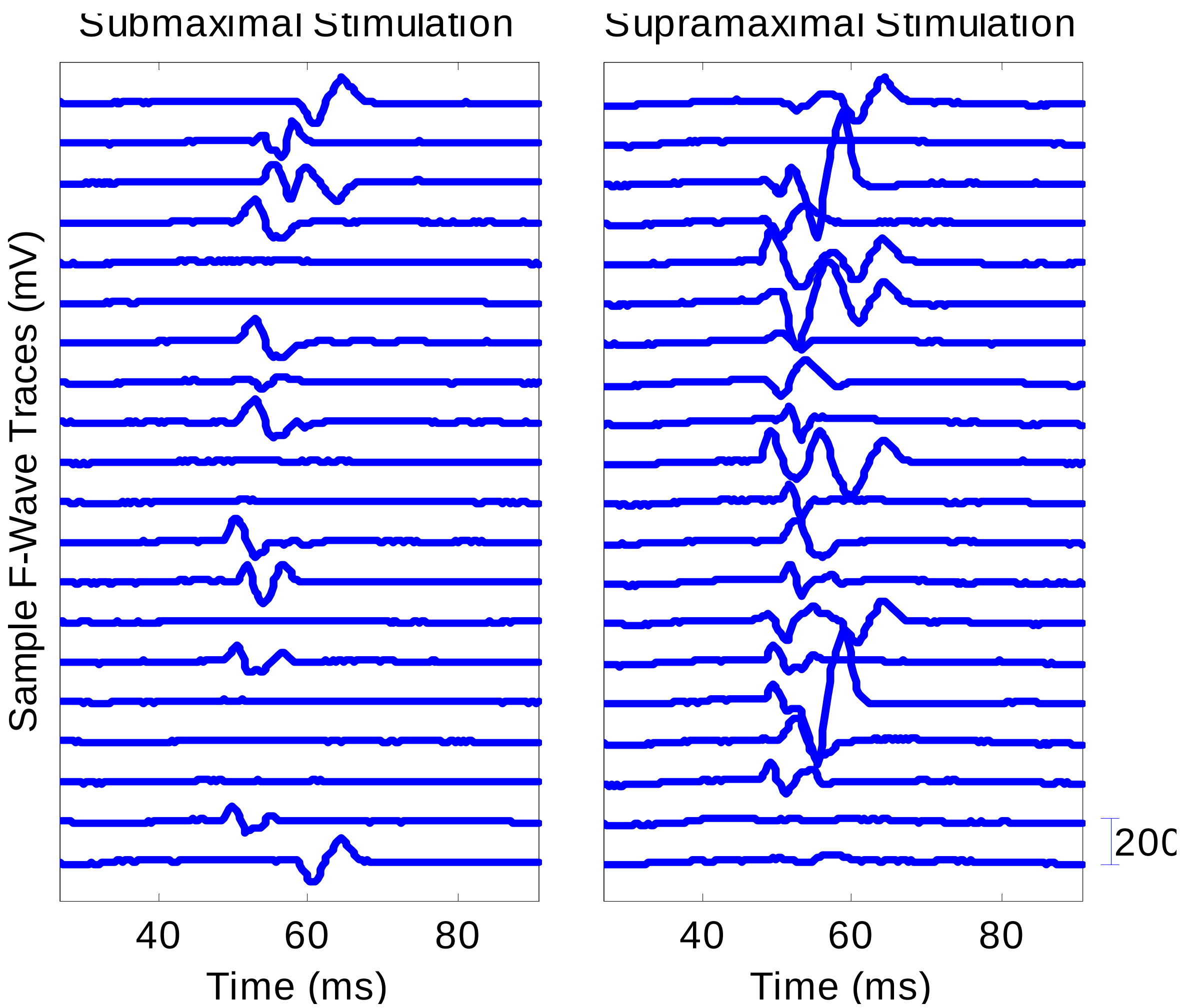

Figure 3. F-wave sample waveform set from same peroneal nerve under submaximal and supramaximal stimulation conditions. In this example, F-wave components had shorter durations under submaximal stimulation condition. Maximum F-wave latency for the submaximal stimulation set is later than its counterpart for supramaximal stimulation set. The F-wave component from slowest conducting fiber (top trace on both subplots) was masked by an earlier component in supramaximal stimulation case thus the measured maximum F-wave latency was earlier than the maximum F-wave latency for submaximal stimulation case.

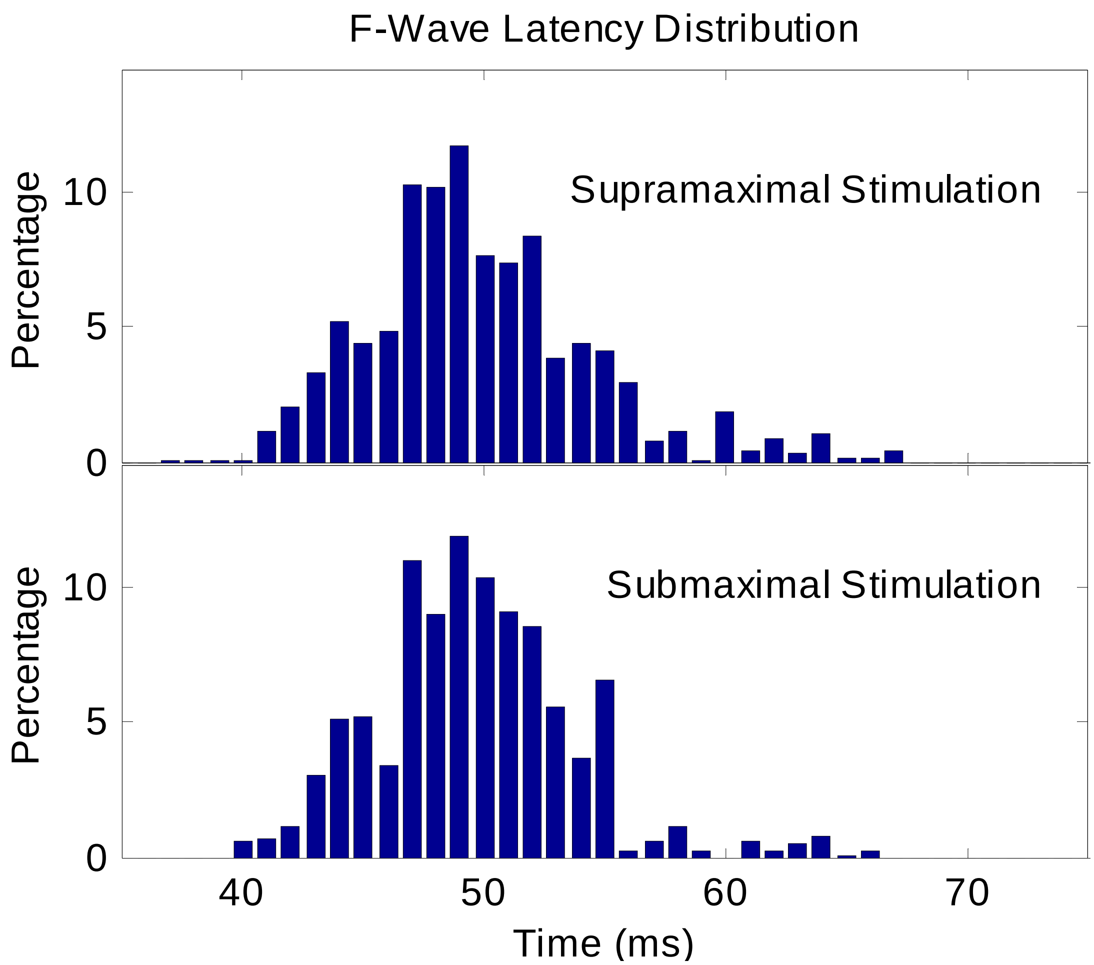

Figure 4. Latency distributions of all recorded F-wave traces acquired under submaximal (bottom panel) and supramaximal (top panel) stimulation are similar to each other.

DISCUSSION

F-wave studies have been established as a valuable tool in clinical neurophysiology (Fisher, 2003). The most robust F-wave parameter is the mean F-wave latency and a reliable estimate requires individual latencies accumulated via 10 or more stimuli depending upon the persistence (Fisher, 1992; Chroni, 1994). Other F-wave parameters such as minimum F-wave latency and chronodispersion require a higher number of stimuli that would yield about 40 F-waves (Chroni, 1994). Repetitive supramaximal stimulation is uncomfortable for many patients. A recent study (DiBenedetto, 2003) demonstrated that low intensity stimulation to the median nerve (10mA vs. 100mA) led to a statistically significant decrease in perceived discomfort level. A more comfortable stimulation scheme would facilitate the accumulation of more F-wave traces that in turn should improve the reliability of F-wave studies.

When the axons of motor neurons are stimulated, the antidromically traveling impulses activate a subset of motor neurons in the anterior horn cells of the spinal cord, a phenomenon known as backfiring. It is believed that both excitatory and inhibitory input levels influence the backfiring of motor neurons. Backfiring action potential impulses then propagate orthodromically along the motor axons, activating muscle fibers where F-waves are recorded. Submaximal stimulation of the distal nerve segment activates fewer motor axons than supramaximal stimulation. Debate persists on whether submaximal stimulation preferentially activates the fastest conducting large-diameter alpha motor neurons (Kimura, 1984; Guiloff, 1991; Panayiotopoulos, 1996). Nevertheless, in this study, the cumulative distributions of all F-wave latencies from all 35 nerves were very similar under submaximal and supramaximal stimulation as shown in Figure 4. Using a robust definition of minimum F-wave latency (5^{th} percentile of all latencies), we did not observe any statistically significant changes in minimum F-wave latency or mean F-wave latency when submaximal and supramaximal results were compared. Maximum F-wave latencies were also compared under the two stimulation conditions and demonstrated no statistically significant difference.

F-wave amplitudes were lower under submaximal stimulation and the differences were statistically significant. In comparison to supramaximal stimulation, submaximal stimulation activates fewer motor fibers peripherally which could lead to alteration in the excitability state of the segmental motor neuron pool. As such, the recorded muscle responses from the backfiring population of motoneurons may not reach the same F-wave detection threshold as frequently as the responses from supramaximal stimulation. Consequently, the F-wave persistence under submaximal stimulation may be lower than the persistence with supramaximal stimulation. Indeed, submaximal stimulation resulted in a statistically significant reduction of persistence. Therefore, clinical interpretation of submaximal stimulation persistence must be made in the context of a submaximal reference range (Fisher, 1980; Voulgaris, 1996; Lin, 2004). Lower persistence may require that a higher number of submaximal stimuli be delivered in order to accumulate sufficient number of F-waves for F-wave parameter estimation. Reduction of the persistence from 65% to 48% implies that additional 11 stimuli were needed to accumulate 20 F-wave latencies under submaximal stimulation condition. For patients whose submaximal peroneal nerve persistence is very low, it may be advantageous to probe the nerves with supramaximal stimulation to see if a significantly higher F-wave persistence is evident. Submaximal stimulation may also increase the probability of axon-reflexes. An automated algorithm is available to identify axon-reflexes (Kong, 2003). When axon-reflexes are detected, supramaximal stimulation may be needed to differentiate them from A-waves that have greater clinical value (Bischoff, 1996). H-reflexes are also a possible complication with submaximal stimulation but are unlikely to appear in late waves recorded from extensor digitorum brevis muscle (Fisher, 1992).

Submaximal stimulation was utilized in prior studies to elicit F-wave responses. Median nerve F-waves were acquired with submaximal stimulation that was sufficient to elicit a CMAP with amplitude 10—20% of the supramaximal CMAP response (DiBenedetto, 2003). They concluded based on 30 subjects that there were no statistically significant differences for mean and minimum F-wave latency, chronodispersion, and persistence. An earlier study examined the effect of 25% and 50% submaximal stimulation on several median nerve F-wave latency parameters (Clinchot, 1994). No significant differences were found for mean F-wave latency, F-wave amplitude, and persistence. Results of the present study are consistent with these earlier studies in that no statistically significant differences were found between submaximal and supramaximal F-wave latencies. Persistence and F-wave amplitude under submaximal stimulation condition were lower with statistical significance in this study and in at least another study (Kimura, 1984) while other studies reported no statistically significant difference (Clinchot, 1994; DiBenedetto, 2003). This disparity may be related to the different nerves studied (median vs. peroneal nerves) or methodological differences. F-wave persistence in this study was determined with a computer algorithm with a fixed F-wave amplitude detection threshold that may have allowed for a more reliable, consistent recording of F-waves than the manual assignments used in previous studies.

Since supramaximal and submaximal tests were two separate F-wave acquisition events, difference between the mean F-wave latencies can be evaluated in the context of test-retest variability. Kohara and colleagues (2000) reported tibial F-wave latency repeatability measures. Each nerve was evaluated twice with a time interval of 1—2 weeks by the same examiner. The results reported were aggregate measures from 32 neurophysiology laboratories. The ICC value of 0.976 in this study was comparable to their reported value of 0.92 for healthy subjects. The present RIV 5-95th percentile value range of [-2.2%, 3.5%] also compares favorably to those reported by Kohara and colleagues (2000), which were [-4.6%, 5.7%] for healthy subjects. Previous analyses of submaximal F-wave parameter properties were generally limited to paired t-test and Pearson correlation coefficient. In addition to these standard analyses submaximal and supramaximal F-wave parameter comparison was framed within a test-retest repeatability context in this study. Additional data analyses were performed to evaluate F-wave parameter characteristics for the two stimulation paradigms.

Several limitations are noted for this study. Subjects were healthy volunteers. In order to gain wide acceptance, submaximal stimulation F-wave analysis must be validated in a neuropathy population meeting clear clinical and electrophysiological criteria. F-wave parameters were compared for nerves with 10 or more F-wave responses (out of 60 stimuli) and results may be different for those subjects with very low persistence. It may be more efficient to revert back to supramaximal stimulation for these subjects. This study evaluated peroneal nerve physiology under submaximal conditions. Similar studies should be performed for other motor nerves. Comparison with the earlier study (Kohara, 2000) in the context of test-retest repeatability was also limited as the tibial nerve retests in the prior study occurred 1—2 weeks apart while peroneal nerve retests in this study occurred within half an hour.

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