REPEATER F-WAVES ARE SIGNS OF MOTOR UNIT PATHOLOGY IN POLIO SURVIVORS

AKIKO HACHISUKA, MD,[1] **TETSUO KOMORI, MD, PhD,**[2] **TATSUYA ABE, MD, PhD,**[2] and **KENJI HACHISUKA, MD, PhD**[1]

[1] Department of Rehabilitation Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi, Kitakyushu 807-8555, Japan
[2] National Hakone Hospital, Odawara, Japan

ABSTRACT: *Introduction:* The purpose of this study was to determine whether F-waves reveal electrophysiological features of anterior horn cells in polio survivors. *Methods:* Forty-three polio survivors and 20 healthy controls underwent motor nerve conduction studies of the median and tibial nerves bilaterally, including sampling of F-waves elicited by 100 stimuli and the determination of motor unit number estimation (MUNE). *Results:* A significant increase in abnormally stereotyped ("repeater") F–waves and a reduction of F-wave persistence were observed in both nerves in the polio group as compared with the control group. Repeater F-waves had a negative correlation with MUNE. *Conclusions:* These trends in F-wave persistence and repeater F-waves after motor unit loss are characteristic findings in polio survivors. Repeater F-waves are a sign of motor unit pathology.

Muscle Nerve **51**: 680–685, 2015

Poliomyelitis is characterized by destruction of anterior horn cells of the spinal cord and motor nuclei of the brainstem, resulting in flaccid paralysis.[1] Although partial or complete functional recovery is often confirmed after acute poliomyelitis, polio survivors whose neuromuscular symptoms have been stable for 2 or more decades may develop post-polio syndrome (PPS), characterized by new muscle weakness, fatigue, pain, and other symptoms.[2–4] PPS is a major problem that limits activities of daily living and social activities.

Studies of the motor units of patients with polio have revealed an ongoing denervation-reinnervation process.[5] This process probably starts after the acute phase of poliomyelitis and, over time, leads to increased motor unit areas caused by collateral sprouting of adjacent motor neurons in the spinal cord.[6] However, the underlying pathophysiology of PPS is still unclear.

To date, there have been only a few reports of nerve conduction studies in polio survivors. McComas et al.[7] reported a 13.4% reduction in the motor unit number estimation (MUNE) and an 18.4% decrease in compound muscle action potential (CMAP) amplitude after a 2-year interval. Sorenson et al.[8] also reported that long-term polio survivors had a modest decline in the summed CMAP amplitude and MUNE. Although MUNE and CMAP amplitudes are useful parameters that can be used to evaluate motor neuron loss, they may not be a direct indication of dysfunction or instability in anterior horn cells.

F-waves are produced by antidromic activation of motor neurons and are characterized by variable amplitude, latency, and waveform. F-waves may indicate dysfunction of anterior horn cells damaged by polio, and thus may predict the onset and progression of PPS. We therefore hypothesized that F-waves would be a useful neurophysiological parameter for probing dysfunction of anterior horn cells in polio survivors. The aims of this study were to: (1) identify the characteristics of F-waves in polio survivors; and (2) demonstrate the relationship between F-waves and MUNE.

METHODS

Subjects. The subjects included in this study were 43 polio survivors (polio group) and 20 healthy controls (control group). The polio group was selected from 110 registered polio survivors who had joined the annual free health examination organized by the local polio patient association and our department based on the following inclusion criteria: (1) a previous history of polio infection diagnosed at a hospital or an official certificate of physical disability induced by polio; (2) between age 50 and 80 years; (3) no musculoskeletal diseases that damage the spinal cord or peripheral nerves; (4) no neurological diseases except polio; and (5) no metabolic diseases that would affect the peripheral nervous system. The polio group consisted of 25 men [age 58.4 ± 5.1 years, height 164.8 ± 8.1 cm (mean $\pm$ SD)] and 18 women (age 60.8 ± 6.1 years, height 152.3 ± 7.8 cm) who had contracted the disease in early childhood, 20 of whom were diagnosed with PPS based on previously reported criteria.[6] The control group, which was age- and

height-matched to the polio group and had neither musculoskeletal, neurological, or metabolic diseases, consisted of 8 men (age 62.9 ± 3.6, height 165.5 ± 6.1 cm) and 12 women (age 58.6 ± 5.3, height 158.2 ± 4.8 cm).

The National Rehabilitation Hospital (NRH) Classification[9] was used to evaluate the severity of flaccid paralysis. The NRH Classification is a limb-specific exercise classification for PPS and is an indicator of the extent of upper and lower extremity impairments. It is used in combination with the medical history, physical examination, and electrodiagnostic examinations. This system categorizes class I as no clinical polio; class II, subclinical polio; class III, clinically stable polio; class IV, clinically unstable polio; and class V, severely atrophic polio.

The study protocol and procedures were approved by the local ethics committee for clinical research. All subjects gave informed, written consent to participate in this investigation and in the electrophysiological examinations.

Methodology. Neurological and physical examinations were performed before the electrophysiological examinations. Subjects in the polio and control groups underwent motor conduction studies and F-wave examinations of the median and tibial nerves bilaterally. Thirty subjects in the polio group and 14 in the control group underwent MUNE examinations of these nerves. Distal motor latency (DML), baseline-to-peak CMAP amplitude, and motor conduction velocity (MCV) were measured and recorded (Synergy N2PIU; Care Fusion Japan, Tokyo).

For measurements of the median nerve, a surface disk electrode was placed on the belly of the abductor pollicis brevis (APB) muscle for recording and on the tendon for reference. A ground electrode was placed between the recording and stimulating electrodes. Stimulation was performed at the wrist (7 cm from the recording electrode) and the elbow. For measurements of the tibial nerve, a surface disk electrode was placed on the motor point of the abductor hallucis muscle (AH) for recording and on the tendon for reference. A ground electrode was placed between the recording and stimulating electrodes. The nerve was stimulated at the ankle (10 cm proximal from the recording electrode) and popliteal fossa. The skin surface temperature of the studied limbs was maintained at $>32°C$.

F-Wave Examinations. One hundred consecutive supramaximal stimuli were delivered at a frequency of 1 Hz to the studied nerves,[10] and the resulting F-waves were stored for subsequent analysis. Filter settings were 3 Hz to 10 kHz, sweep speed was 5 or 10 ms per division, and the amplifier gain was 0.2–0.5 mV per division. The following F-wave parameters were obtained: minimal latency; mean amplitude; persistence (FP); conduction velocity; and occupancy rate of repeater F-waves (ORF). The amplitude of each F-wave from baseline to peak was measured manually if the amplitude was ≥ 10 µV. Repeater F-waves, which were waves with identical latency, amplitude, and waveform, were detected by visual inspection. The ORF was defined as the number of repeater F-waves divided by the total number of F-waves, expressed as a percentage.

MUNE Examinations. The multiple point stimulation technique[11] was used to estimate the motor unit number of the APB and AH. The maximum CMAP amplitude was recorded, and 10 different individual single motor unit action potentials (s-MUAPs) were obtained by moving the stimulating electrode and isolating threshold responses with distinct morphologies. The MUNE was determined by dividing the mean amplitude of s-MUAPs into the CMAP amplitude evoked in the same muscle.

Statistical Analyses. The distribution of NRH classes in this study and in registered polio survivors at our hospital were compared using the chi-square test. Parametric variables are expressed as mean and standard deviation. The mean values of parametric variables between the groups were compared using the Student t-test. The relationship between the FP and ORF was assessed using a regression analysis. Statistical significance was set at $P < 0.01$. All analyses were performed using SPSS for Windows (version 19.0) software (SPSS, IBM, Tokyo, Japan).

RESULTS

NRH of the Polio Survivors. The 86 upper limbs and 86 lower limbs of the polio survivors were separated into 5 classes based on the NRH Classification. Three fourths of the upper limbs were classified as having no or subclinical polio, whereas $>80\%$ of the lower limbs were classified as clinically stable, clinically unstable, or severely atrophic. The distribution of classes was the same as that of registered polio survivors (Table 1).

Comparisons of F-Wave Variables between Polio Survivors and Healthy Subjects. F-waves could be obtained from 82 of 86 upper limbs and from 76 of 86 lower limbs. The DMLs, MCVs, F-wave conduction velocities, and F-wave amplitudes were not significantly different between the polio and control groups (Tables 2 and 3). The CMAP amplitude and FP (%) were significantly lower in the polio group than in the control group. The F-wave minimal latency of the median nerve was

Table 1. National Rehabilitation Hospital Classification of limbs in polio survivors.

	Upper limbs		Lower limbs	
NRH Classification	This study ($n = 86$)	Registered polio survivors ($n = 220$)	This study ($n = 86$)	Registered polio survivors ($n = 220$)
I	58 (67.4%)	161 (73.2%)	10 (11.6%)	41 (18.9%)
II	7 (8.1%)	11 (5.0%)	2 (2.3%)	17 (7.7%)
III	14 (16.3%)	36 (16.4%)	19 (22.1%)	52 (23.6%)
IV	6 (7.0%)	3 (1.4%)	18 (20.9%)	27 (12.3%)
V	1 (1.2%)	9 (4.1%)	37 (43.0%)	83 (37.7%)

significantly prolonged in the polio group as compared with the control group. The polio group had a significantly larger total number of repeater F-waves and higher ORFs than did the control group. The MUNEs of the APB and AH were significantly decreased compared with those of the control group.

Correlation of Repeater F-Waves and MUNE in Polio Survivors. Both F-waves and MUNEs were obtained from 54 limbs in the polio group. ORF and MUNE were significantly negatively correlated (Fig. 1).

Correlation of Repeater F-Wave Occupancy and F-Wave Persistence. On scatterplots of the FP and ORF of polio survivors, a high FP tended to be associated with a low ORF, especially in the tibial nerve (Fig. 2). The normal ranges of the FP were from 49.7% to 100% (mean -2 SD) in the median nerve and always 100% in the tibial nerve; the normal ranges of the ORF were from 0% to 25.4% (mean $+2$ SD) in the median nerve and from 0% to 3.8% (mean $+2$ SD) in the tibial nerve. Only 28.0% of upper limbs and 10.5% of lower limbs in the polio survivors had both normal FP and normal ORF.

DISCUSSION

The results obtained from this study indicate that the characteristic findings of the F-waves evoked in the polio survivors were occurrence of

repeater F-waves, reduction of FP, and increase in ORF. ORF had a negative correlation with MUNE.

The distributions of the NRH classes in this study were in line with those of registered polio survivors, and these subjects were considered members of a typical group of polio survivors in Japan. This study was also similar to the NRH profile of 60 polio survivors in the USA reported by Gawne.[9]

The characteristic finding of F-waves in polio survivors was abundant repeater F-waves with a high occupancy rate. The occurrence of repeater F-waves has been demonstrated in carpal tunnel syndrome,[12] motor neuron disease,[13] cervical spondylosis,[14] lumbosacral radiculopathy,[15] and Guillain-Barré syndrome.[16] The ORFs of the polio group were approximately 4-46 times greater than those of the control group.

The mechanisms of the production of repeater F-waves have not been completely elucidated, but it has been inferred that loss of motor neurons is the most important factor. In polio survivors, the ongoing denervation-reinnervation process continues for more than 20 years and, consequently, an increase in repeater F-waves may be more characteristic of these patients than of patients with other causes of neurogenic atrophy. Decreasing excitability of some anterior horn cells or loss of motor units may induce the remaining anterior horn cells to produce repeater F-waves, or particular anterior horn cells with increased excitability may produce repeater F-waves. The aging process[17] is also

Table 2. Comparisons of motor nerve conduction, F-wave values, and MUNEs in median nerves of the polio and control groups.

	Median nerve		
Variable	Polio	Control	P
DML (ms)	4.4 ± 4.2	3.6 ± 0.6	0.241
CMAP amplitude (mV)	5.1 ± 2.8	6.7 ± 2.5	0.006
MCV (m/s)	58.4 ± 7.3	60.1 ± 3.6	0.225
F-wave persistence (%)	60.7 ± 27.5	79.5 ± 14.9	<0.001
F-wave minimum latency (ms)	25.7 ± 2.9	23.8 ± 1.6	<0.001
F-wave mean amplitude (μV)	113.4 ± 71.0	89.4 ± 39.4	0.071
F-wave conduction velocity (m/s)	66.5 ± 7.4	68.9 ± 4.3	0.082
Total number of repeater F-waves	21.9 ± 15.6	8.0 ± 5.6	<0.001
Occupancy rate of the repeater F-waves (%)	41.3 ± 26.6	10.6 ± 7.4	<0.001
MUNE	96.9 ± 84.4	224.1 ± 63.4	<0.001

Values presented as mean ± standard deviation.

Table 3. Comparisons of motor nerve conduction, F-wave values, and MUNEs in tibial nerves of the polio and control groups.

	Tibial nerve		
Variable	Polio	Control	P
DML (ms)	3.8 ± 1.0	3.4 ± 0.6	0.017
CMAP amplitude (mV)	6.9 ± 5.8	13.1 ± 4.7	<0.001
MCV (m/s)	50.0 ± 8.0	49.7 ± 5.6	0.837
F-wave persistence (%)	84.4 ± 28.1	100.0 ± 0.0	<0.001
F-wave min latency (ms)	44.6 ± 4.8	44.0 ± 3.7	0.491
F-wave mean amplitude (μV)	162.9 ± 94.6	144.6 ± 63.9	0.280
F-wave conduction velocity (m/s)	55.8 ± 6.8	58.2 ± 6.2	0.075
Total number of repeater F-waves	17.9 ± 19.8	1.0 ± 1.7	<0.001
Occupancy rate of the repeater F-waves (%)	27.9 ± 31.8	0.6 ± 1.6	<0.001
MUNE	186.7 ± 184.8	387.4 ± 151.0	<0.001

Values presented as mean ± standard deviation.

thought to increase motor neuron excitability, leading to enhanced production of repeater F-waves. Thus, as motor neurons are lost, the probability of F-waves with varying shapes may diminish, and repeater F-waves from individual motor units may come to be recognized more easily.[14]

We have found a negative correlation between repeater F-waves and MUNE in polio; repeater F-waves appear to be a useful sign of motor unit loss. This conclusion is supported by a previous study on motor neuron disease.[14]

Argyriou et al. reported F-wave abnormalities in amyotrophic lateral sclerosis (ALS)[18] that included reduced FP, prolonged F-wave latencies, and higher F-wave amplitudes. F-wave abnormalities in the polio survivors in our study were similar to those found in ALS, and we can speculate that the same underlying mechanism produces the F-wave abnormalities in both diseases. Concerning findings on minimal F-wave latencies, the pathophysiol-

ogy underlying the ALS phenotype[18] probably causes preferential loss of fast-conducting fibers, and the same mechanism may contribute to the slight prolongation of F-wave latencies in PPS. The presence of large post-reinnervation motor unit potentials due to lower motor neuron dysfunction could explain the increase in amplitude of F–waves in ALS[19]; however, no significant changes in F-wave amplitudes were seen in our study. We suspect that a difference in F-wave amplitude between polio survivors and patients with ALS derives from variations of upper motor neuron dysfunction[18] and disease progression.

We found that the correlation between repeater F-waves and MUNE was more evident in the tibial nerve than in the median nerve. We believe there are 2 reasons for this: specificity of the nerves and a difference in disease severity between upper and lower limbs. Only 32.6% of upper limbs in our subjects were clinically
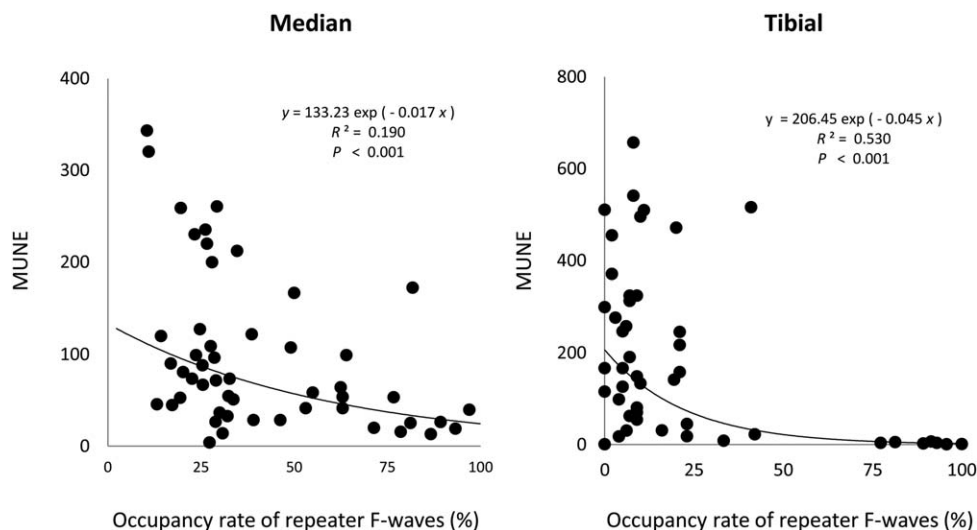

Median

$y = 133.23 \exp(-0.017x)$
$R^2 = 0.190$
$P < 0.001$

Tibial

$y = 206.45 \exp(-0.045x)$
$R^2 = 0.530$
$P < 0.001$

FIGURE 1. Correlations between the occupancy rate of repeater F-waves and the MUNE. The correlation coefficients (*r*) of the relationships are shown.
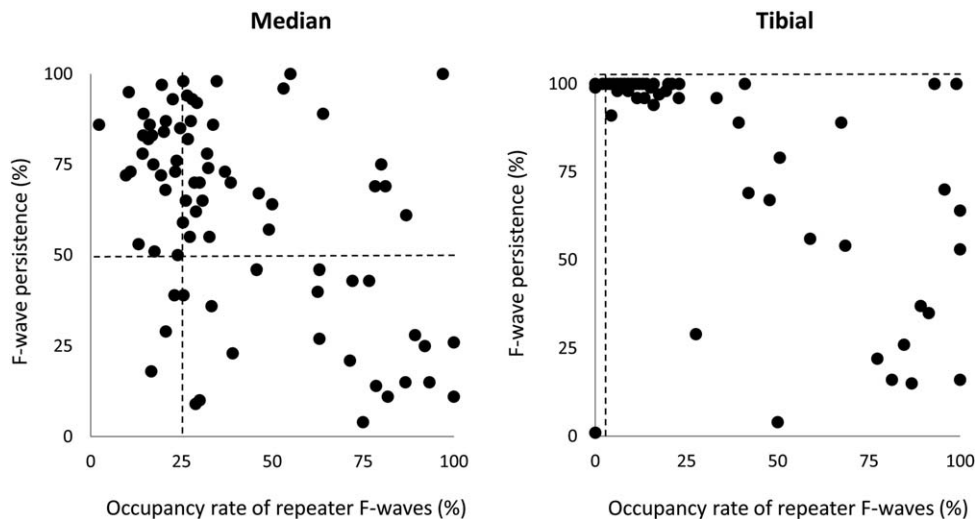
Median

Tibial

FIGURE 2. Scatterplots showing individual values. The lower limit (mean - 2 SD) for F-wave persistence in the control group and the upper limit (mean + 2 SD) for the occupancy rate of repeater F-waves in the control group are indicated with dashed lines.

symptomatic, whereas 88.3% of lower limbs were clinically symptomatic. On the other hand, Wohalfart[20] reported that up to 30% of ventral horn cells may be lost before clinical symptoms become evident, so some degree of neuronal dropout could be expected in the majority of our patients. F-waves may detect subtle changes even in patients without clinical symptoms whose anterior horn cells may have been subclinically damaged by the initial poliomyelitis. F-wave characteristics may therefore reveal subclinical alterations and should be a helpful measure for evaluating the risk of PPS.

Analyzing F-waves, especially repeater F-waves and variations in F-waveforms, may provide a new approach to motor unit evaluation. This may be a useful evaluation method not only for polio survivors, but also for patients with other neurogenic diseases involving motor units. Computerized automation for identification of repeater F-waves is necessary for further investigation and clinical application. We have already begun studies to develop this automation.[21,22]

Our study has 2 limitations. First, MUNE for the AH is not a popular method. However, we were able to obtain AH MUNE using a comparatively easy technique, and the values were significantly different between the polio and control groups. Second, the study was cross-sectional, and the long-term changes in F-waves in polio therefore remain unknown.

In conclusion, the characteristic features of F-waves in polio survivors were the occurrence of repeater F-waves, an increase in ORF, and a reduction of FP. ORF correlated negatively with MUNE. Certain F-waves, especially repeater F-waves, are signs of motor unit pathology in polio survivors.

REFERENCES

1. Jubelt B, Miller JR. Viral infections. In: Rowland LP, editor. Merrit's textbook of neurology, 9th ed. Baltimore: Williams & Wilkins; 1995. p 142–179.
2. Dalakas M, Elder G, Hallett M, Ravits J, Baker M, Papadopoulos N, et al. A long-term follow-up study of patients with post-poliomyelitis neuromuscular symptoms. N Engl J Med 1986;314:959–963.
3. Agre JC, Rodriquez AA, Tafel JA. Late effects of polio: critical review of the literature on neuromuscular function. Arch Phys Med Rehabil 1991;72:923–931.
4. Gonzalez H, Sunnerhagen KS, Sjoberg I, Kaponides G, Olsson T, Borg K. Intravenous immunoglobulin for post-polio syndrome: a randomized control trial. Lancet Neurol 2006;5:493–500.
5. Grimby G, Stalberg E, Sandberg A, Sunnerhagen KS. An 8-year longitudinal study of muscle strength, muscle fiber size, and dynamic electromyogram in individuals with late polio. Muscle Nerve 1998;21:1428–1437.
6. Gonzales H, Olsson T, Borg K. Management of postpolio syndrome. Lancet Neurol 2010;9:634–642.
7. McComas AJ, Quartly C, Griggs RC. Early and late losses of motor units after poliomyelitis. Brain 1997;120:1415–1421.
8. Sorenson EJ, Daube JR, Windebank AJ. Electrophysiological findings in a cohort of old polio survivors. J Peripher Nerv Syst 2006;11:241–246.
9. Gawne AC. Strategies for exercise prescription in post-polio patients. In: Halster LS, Grimby G, editors. Post-polio syndrome. Philadelphia: Hanley & Belfus; 1994. p 141–164.
10. Suzuki K, Masakado Y, Abe L, Ota T, Kimura A. The anterior horn cell excitability estimation by F waves: effect number of stimuli. J Clin Neurophysiol 2009;37:441–445.
11. Doherty TJ, Brown WF. The estimated numbers of relative size of thenar motor units as selected by multiple point stimulation in young and old adults. Muscle Nerve 1993;16:355–366.
12. Petajan JH. F-wave in neurogenic atrophy. Muscle Nerve 1985;8:690–696.
13. Macleod WN. Repeater F-waves: a comparison of sensitivity with sensory antidromic wrist-to-palm latency and distal motor latency in the diagnosis of carpal tunnel syndrome. Muscle Nerve 1987;37:773–778.
14. Peioglou-Harmoussi S, Fawcett PR, Howel D, Barwick DD. F-response frequency in motor neuron disease and cervical spondylosis. J Neurol Neurosurg Psychiatry 1987;50:593–599.

15. Pastore-Olmedo C, Gonzalez O, Geijo-Barrientos E. A study of F-waves in patients with unilateral lumbosacral radiculopathy. Eur J Neurol 2009;16:1233–1229.
16. Geijo-Barrientos E, González O, Pastore-Olmedo C. Case report. Presence of repeater F-waves in the early stage of Guillain-Barré syndrome. J Peripher Nerv Syst 2012;17:128–131.
17. Chroni E, Tendero IS, Punga AR, Stalberg E. Usefulness of assessing repeater F-waves in routine studies. Muscle Nerve 2012;45:477–485.
18. Argyriou AA, Polychronopoulos P, Talelli P, Chroni E. F wave study in amyotrophic lateral sclerosis: assessment of balance between upper and lower motor neuron involvement. Clin Neurophysiol 2006;117:1260–1265.
19. Drory VE, Kovach I, Groozman GB. Electrophysiological evaluation of upper motor neuron involvement in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 2001;2:147–152.
20. Wohalfart G. Collateral regeneration from residual motor nerve fibers in ALS. Neurology 1957;7:124–134.
21. Honda A, Fukuda R, Hachisuka A, Hachisuka K. Comparison of baselines in analysis of F-responses. In: Proceedings of the 9th International Conference on Modeling Decisions for Artificial Intelligence; 2012. p 34–39.
22. Fukuda R, Honda A, Hachisuka A, Hachisuka K. Comparison of baseline in extraction of F-responses. J Adv Comput Intel Intellig Inform 2013;17:535–539.