

Reappraisal of the F/M amplitude ratio in carpal tunnel syndrome

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Summary

The F-wave/M-wave amplitude (F/M-amp) ratio has been shown to be increased in peripheral neuropathies, provided the maximum M-wave is relatively preserved. Reduced M-wave amplitudes and central facilitation of antidromically-induced reactivation of the anterior horn cells' axon hillocks (F-wave) are believed to contribute to higher F/M-amp ratios. The present study was undertaken to re-evaluate mechanisms responsible for higher F/M-amp ratios in carpal tunnel syndrome (CTS). We enrolled 232 cases affected by CTS and 108 controls. F- and M-wave amplitudes and F-wave chronodispersion were analyzed for the median and ulnar nerves. The F/M-amp ratio of the median nerve in CTS subjects with moderate-severe nerve damage was significantly higher than that of mild CTS subjects and controls. Chronodispersion of the median nerve F-wave increased with increasing CTS severity. We conclude that the relative preservation of the median nerve F-wave is due to damage to the large diameter muscle afferent fibers responsible for the monosynaptic response. Absence of the monosynaptic response makes the small motoneurons, usually inaccessible to the antidromic volley because of its collision with the orthodromic reflex volley, able to fire in the F-wave.

KEY WORDS: *carpal tunnel syndrome, F-wave, Ia afferents, motoneurons, neuropathy.*

Introduction

The F-wave/M-wave amplitude (F/M-amp) ratio provides a measure of the proportion of a motoneuron pool activated in a series of F-waves.

The neurophysiological mechanism underlying the production of F-wave responses is antidromic activation of the peripheral motor fibers resulting in recurrent discharges ("backfiring") of a small number of motoneurons (MNs). Briefly, once the antidromic volley reaches the somadendritic membrane, the resulting transmembrane depolarizing current may reactivate the axon hillock, i.e. the specialized region near the start of the axon where

clusters of sodium channels generate action potentials (Eccles, 1955; Brown, 1968). Therefore, F-wave production is dependent on the state of the peripheral nervous system, as well as on MN pool excitability (Lin and Floeter, 2004; Fisher, 1988a, 2007; Rossi et al., 2012). F-wave changes have been documented in mononeuropathy (Fisher, 1988a; Panayiotopoulos and Chroni, 1996; Aygül et al., 2014), upper and lower MN disease (Argyropoulos et al., 1978; Eisen and Odusote, 1979; Fisher, 2007), and also during and after natural activity (Rossi et al., 2012; Khan et al., 2012).

Although increased F/M values are frequently found in neuropathies, the significance of this measurement in peripheral nerve disorders has not been defined. Both reduced M-wave amplitudes and central compensation for peripheral nerve damage are believed to contribute to higher F/M-amp ratios (McDonald, 1963; Fisher, 2007; Aygül et al., 2014). Central compensation alludes to the possibility that the less marked reduction in the F-wave compared with the M-response (i.e. the relative preservation of the F-wave) is attributable to increased excitability of MNs. Indeed, from the perspective of the consequences of a nerve injury, the peripheral and central nervous systems are functionally integrated, and functional deficits caused by peripheral nerve damage always result in long-lasting remodeling of central nervous system circuitry related to the lost functions (Navarro et al., 2007).

The present study aims to clarify the mechanisms responsible for the increased F/M-amp ratio in carpal tunnel syndrome (CTS). The relationship between the F-wave and the M-wave was studied in 232 idiopathic CTS subjects. We reviewed the database of a previous study conducted with another aim (Mondelli and Aretini, 2015).

Materials and methods

In our previous prospective study, we reported clinical and electrophysiological findings in 244 CTS subjects and 108 controls consecutively enrolled at an EMG lab (Mondelli and Aretini, 2015). CTS diagnosis was made on the basis of clinical findings in accordance with the recommendations of the American Academy of Neurology (Quality Standards Subcommittee of the AAN, 1993). We excluded from cases and controls all subjects who met any of the following exclusion criteria: previous surgery of the upper limb, radiculopathy, mononeuropathy or plexopathy of the arm, polyneuropathy, amyotrophic lateral sclerosis, diabetes, rheumatic or thyroid diseases, renal failure, a history of alcoholism and central nervous system diseases, malignancy in the previous 5 years, and previous intake of medication considered toxic to the peripheral nervous system. Therefore, only subjects whose clinical examination and electrodiagnosis were negative for neuromuscular diseases were included in the controls.

The electrophysiological methods are already reported in detail elsewhere (Mondelli and Aretini, 2015). In brief, the electrophysiological study consisted of measuring elbow-wrist motor conduction velocity, distal motor latency (DML) calculated for a distance of 7 cm between stimulating and recording points, and compound muscle action potential (CMAP) amplitude (measured from baseline to negative peak) of the median nerve from the abductor pollicis brevis (APB) muscle, and of the ulnar nerve from the abductor digiti minimi (ADM) muscle. Orthodromic sensory conduction velocity (SCV) and sensory action potential (SAP) amplitude were recorded in the median nerve in the third finger-wrist and fourth finger-wrist tracts, and in the ulnar nerve in the fourth finger-wrist tract (U4). F-waves were evoked in the APB and ADM MNs by 25% supramaximal stimulation applied at the wrist at 0.5 Hz. Twenty consecutive stimuli were used to obtain F-waves. The traces were reviewed visually and only appropriately timed and morphologically reproducible deflections were accepted as F-waves.

We were quite confident that axon reflexes and H-reflexes were not included in the F-waves. Indeed, contamination of the F-waves with H-reflexes and axon reflexes can be avoided with supramaximal stimulation (Panayiotopoulos and Chroni, 1996). Moreover, unlike F-waves, axon reflexes have a constant latency and waveform, and they may rarely appear within the latency territory of F-waves (Fullerton and Gilliat, 1965).

We only considered F-waves with amplitudes of at least 20 μ V. F-wave amplitudes were measured peak-to-peak while the latency of each F-wave was measured by placing the cursor on the first deflection from the baseline. Several parameters were analyzed, including the percentage mean of F/M-amp ratio and the F-wave persistence, i.e. the number of elicited F-waves / 20 stimuli delivered. The amplitude of each individual F-wave was measured, and then the mean F-wave amplitudes were calculated for each recording series. In addition, chronodispersion, i.e. the difference between the minimal and maximal F-wave latencies, was also measured. In the previous paper we also measured the minimal F-wave latency and the mean of the latencies of all elicited F-waves (Mondelli and Aretini, 2015), but the results of these F-wave parameters are not reported here as they are not relevant to the purpose of the present study. An infrared lamp was used to keep skin temperature of the hand constant above 32°C. The CTS subjects were classified according to a validated scale of electrophysiological CTS severity, with stages ranging from 0 to 5 (Padua et al., 1997).

Patient selection

From the original database, subjects with CMAP amplitudes below 1.5 mV were excluded from the analysis, since below this value F-waves with amplitudes under 20 μ V can easily be obtained. Indeed, the amplitude of individual F-waves usually fluctuates between 1 and 5% of the CMAP (Eisen, 1979; Kimura, 1989) given that the axon hillock is reactivated in only 1-3 MNs in response to the stimulus. At the end of the clinical and electrophysiological examination, each patient was assigned to the first or the second group, on the basis of their electrophysiological CTS severity scale score (Padua et al.,

1997). The first group comprised patients in stages 0-2 on the Padua scale ("mild stage group"), that is, cases with only clinical symptoms and delay of SCV of the median nerve or abnormal comparative median-ulnar nerve conduction study testing with normal DML; the second group included cases in stages 3-4 ("moderate/severe stage" group), that is, patients with delay of DML and SCV or absence of SAP. In the latter group, subjects with CMAP amplitudes below 1.5 mV were eliminated from the study.

Statistical analysis

The data were tested for normal distribution (Kolmogorov-Smirnov distance method). Differences between CTS groups and controls were analyzed with the non-parametric Kruskal-Wallis test; Dunn's multiple comparisons test was used to check the differences between successive pairs of single CTS stage groups. The Mann-Whitney test was used to check differences in chronodispersion between CTS groups. An alpha-error of 0.05 was accepted. Results are presented as mean values and standard deviation (SD).

Results

We enrolled 232 CTS subjects. Applying the electrophysiological scale (see above), 93 CTS cases were allocated to the "mild stage" group (mean age 49.6 \pm 13.5 years, range 24-82, females 74), and 139 CTS cases to the "moderate/severe stage" group (mean age 58.9 \pm 14.5 years, range 24-87, females 97). The control group comprised 108 healthy subjects (mean age 52.4 \pm 16 years, range 19-83, females 75). The mean heights of the subjects in the "mild", "moderate/severe" and control groups were 161.4 \pm 8.3 cm, 161.6 \pm 8.7 cm, and 161.5 \pm 8.7 cm, respectively.

For the median nerve: the F/M-amp ratio (%) was 2.39 \pm 0.7 in controls, 2.42 \pm 0.6 in mild stage, and 2.95 \pm 1.2 in moderate/severe stage (p <0.001); the mean CMAP amplitude (mV) was 11.43 \pm 3.2 in controls, 11.25 \pm 3.1 in mild stage, and 8.43 \pm 3.5 in moderate/severe stage (p <0.001); the mean F-wave amplitude (μ V) was 0.26 \pm 0.07 in controls, 0.26 \pm 0.06 in mild stage, and 0.21 \pm 0.06 in moderate/severe stage (p <0.001); the mean F-wave persistence (number) was 17.74 \pm 2 in controls, 17.31 \pm 2.2 in mild stage, and 15.72 \pm 3.6 in moderate/severe stage (p <0.001); finally, the chronodispersion value was 3.15 \pm 0.9 in controls, 2.99 \pm 0.7 in mild stage, and 3.62 \pm 1.5 in moderate/severe stage (p =0.035). For the ulnar nerve, the F/M-amp ratio (%) was 2.54 \pm 0.6 in controls, 2.48 \pm 0.5 in mild stage, and 2.50 \pm 0.46 in moderate/severe stage (p =0.52). All electrophysiological data are reported in Table 1 with the respective statistical analysis. Because the controls were a little younger and taller than the cases, we also performed another statistical analysis after matching, for age and gender, 100 cases and 100 controls selected from the sample included in the present study. The mean age and mean height of the patients with mild CTS, of those with moderate/severe CTS, and of the controls were not significantly different [161.5 \pm 9,

163.7±8.8 and 162.7±8.9 cm (p=0.31)]; 49.85±15, 55±14, 53.12±15.3 years (p=0.16), respectively)]. The results of F/M-amp ratios were similar to those obtained in the whole sample: the differences concerned only the median nerve but not the ulnar nerve.

Discussion

The ratio of the F-wave amplitude to the corresponding direct muscle response is an estimate of the proportion of an MN pool that is producing F-waves. The present study demonstrated that the amount of the median nerve MNs discharging and thus producing F-waves was significantly increased in subjects with moderate/severe CTS than in those with mild CTS and controls. In moderate/severe CTS, both the F-wave and the M-wave responses of the ulnar nerve were significantly lower than in healthy subjects but their ratio remained within the control values.

It is unlikely that the F/M-amp ratio increase was caused by peripheral factor such as axonal loss or motor unit rearrangement. Indeed we enrolled only subjects with relatively preserved maximum M-potentials (the mean M-wave amplitude of the median nerve was 8.43 mV). Moreover, confirming previous observations (Ginanneschi, et al., 2007), we found that the ADM M-wave evoked by maximal stimulation of the ulnar nerve in moderate/severe CTS was significantly decreased with respect to what was found in mild CTS and controls. This result has been attributed to increased mechanical pressure on the ulnar nerve at the wrist in these patients (Ginanneschi, et al., 2008). Nevertheless, unlike the median nerve ratio, the ulnar nerve F/M-amp ratio remained unchanged.

An alternative hypothesis can be proposed to clarify the mechanism underlying the increase in the F/M-amp ra-

tio observed in CTS. In humans, the antidromic stimulus that is responsible for F-waves reaches the spinal MNs after the monosynaptic excitation, which is transmitted by Ia afferents. The greater the distance between the stimulating electrode and the spinal cord, the more important the higher conduction velocity of the Ia afferents (compared with the synaptic delay between the Ia afferents and the MNs) becomes. In short, afferent-induced action potentials cancel the antidromic invasion, inhibiting the formation of F-waves. F-waves in humans are preferentially generated by recurrent responses of larger and faster-conducting MNs. Analysis of repeater F-wave amplitudes supports the latter assumption (Fisher et al., 1994). This fact is related to a greater chance of collision and mutual extinction of orthodromic (reflex) and antidromic impulses in smaller axons (Mazzocchio et al., 1995; Espiritu et al., 2003). It follows that the hold-back of the monosynaptic response makes a larger number of MNs (i.e. the small ones) able to generate F-waves. This may occur in the case of conduction failure of group Ia afferent fibers. Indeed, it is what may actually occur in CTS, in which it can be hypothesized that, in the moderate/severe stage, the compression of the group I afferent fibers could prevent adequate summation of post-synaptic potentials on MNs, thus preventing their monosynaptic response.

Under this condition, low-threshold MNs may become available for generating F-responses; this will result in increased F-wave amplitudes and consequently higher F/M amp ratios.

Indeed: 1) the large sensory fibers (i.e. group I fibers) responsible for generating the monosynaptic response are especially sensitive to the effects of compression (Zhu et al., 1998; Rossi et al., 1988).

This implies a loss of these fibers in the advanced stages of CTS, in which the pressure within the tunnel is especially high; 2) as shown in the present paper, F-

Table I - Demographic, anthropometric, nerve conduction velocity and F-wave parameters in cases and controls and differences between the two groups.

	Controls (no.108)	Mild CTS (no.93)	Moderate-Severe CTS (no.139)	P values	Dunn's Multiple Comparison Test
Median Nerve					
M-wave amp (mV)	11.43±3.2	11.25±3.1	8.43±3.5	<0.0001	Cont vs Mod-Sev *** Mild vs Mod-Sev ***
F-wave amp (uV)	0.26±0.07	0.26±0.06	0.21±0.06	<0.0001	Cont vs Mod-Sev *** Mild vs Mod-Sev ***
Mean F/M amp ratio (%)	2.39±0.7	2.42±0.6	2.95±1.2	<0.0001	Cont vs Mod-Sev ** Mild vs Mod-Sev *
F chronodispersion (ms)	3.15±0.9	3±0.7	3.62±1.5	0.03	Mild vs Mod-Sev *
F persistence (no.)	17.74±2	17.31±2.2	15.72±3.6	<0.0001	Cont vs Mod-Sev *** Mild vs Mod-Sev **
Ulnar Nerve					
M-wave amp (mV)	11.6±2.2	11.36±1.8	10.8±2.4	0.029	Cont vs Mod-Sev *
F-wave amp (uV)	0.29±0.07	0.28±0.07	0.26±0.06	0.04	Cont vs Mod-Sev *
Mean F/M amp ratio (%)	2.54±0.6	2.48±0.5	2.5±0.46	n.s.	
F chronodispersion (ms)	3.01±0.8	2.88±0.84	2.87±0.7	n.s.	
F persistence (no.)	18.87±1.1	18.58±1.2	18.57±1.3	n.s.	

Abbreviations: Amp: amplitude; CTS: carpal tunnel syndrome; Cont: controls; Mod-Sev: moderate severe stage; n.s.: not significant; no.: number. Results are reported as mean values±standard deviation.

*= p<0.5; **= p<0.01; ***= p<0.001

wave chronodispersion in patients with CTS is significantly higher than in controls. Also, chronodispersion increases with increasing CTS severity. The most immediate explanation is that whereas in normal subjects only large MNs with rapid conduction velocity can generate the F-wave, in patients with CTS both large and small MNs (the latter with slow conduction velocity) can be recruited in the response. It therefore seems reasonable to assume that the increased F/M-amp ratio, due to a relative facilitation of the F-wave in peripheral nerve injury, depends upon the afferent loss in advanced peripheral nerve injury. The unchanged ulnar nerve F/M-amp ratio corroborates our conclusion. Indeed, although a positive correlation between median and ulnar nerve damage in CTS exists, alterations in the ulnar nerve fiber generally correspond to about 1/5 of those occurring in the median nerve, since the pressure increase in Guyon's canal is somewhat less marked than that in the carpal tunnel (Ginanneschi et al., 2008). This implies that ulnar nerve afferent fibers activated by supramaximal stimuli are enough to discharge small MNs monosynaptically, thus preventing their recurrent discharge.

Obviously, the possibility of enhanced spinal cord MN excitability after peripheral nerve damage cannot be categorically excluded (Jaberzadeh and Scutter, 2006; Navarro et al., 2007; Girlanda et al., 2000). In this regard, it is worth mentioning that some papers suggest that the F-wave provides a flawed measure of MN pool excitability (Espirito et al., 2003; Burke, 2014), whereas others indicate that F-waves could be better suited to detecting inhibition than facilitation of MNs (Lin and Floeter, 2004; Rossi et al., 2012), given that the increased H-reflex occurring with higher MN excitability would decrease the number of MNs capable of producing an F response.

On the other hand, an increased mean F/M-amp ratio is a good reflection of spasticity (Fisher, 1988a; Eisen and Fisher, 1999), in which the H-reflex amplitude is generally increased. In conclusion, informed use of F-waves requires an understanding that these responses originate at the interface between the central and the peripheral nervous systems, and that F/M-amp values directly correlate with neuromuscular efficiency. This relationship is disturbed in patients with peripheral nerve dysfunction (Fisher, 1988b).

Even with these limitations, the data in the present paper suggest that progressive damage of the large diameter muscle afferent fibers responsible for the monosynaptic response may contribute to the relative preservation of the F-wave and consequently the higher F/M-amp ratio in CTS.

Regardless of the pathophysiology, from a clinical/diagnostic point of view our data may be useful in the discrimination of CTS severity, increasing the diagnostic yield in CTS.

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