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Comparing sural/radial amplitude ratio and minimal F-wave latency to Conventional Nerve Conduction Studies for the Evaluation of sensitive nerve conduction parameter in type 2 Diabetic patients with Sensorimotor Polyneuropathy

Authors: Arjun Baidya, Mridul Bera, Rishad Ahmed

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ORIGINAL ARTICLE

Arjun Baidya[1] (https://orcid.org/0000-0003-2419-9096), Mridul Bera[2] (https://orcid.org/0000-0002-6530-5978), Rishad Ahmed[3] (https://orcid.org/0009-0003-3640-8083)

[1]Department of Endocrinology, Nil Ratan Sircar Medical College and Hospital, Kolkata, India
[2]NH Narayana Multispeciality Hospital, Howrah, West Bengal, India
[3]Department of Medicine, KPC Medical College and Hospital, Kolkata, India

Comparing sural/radial amplitude ratio and minimal F-wave latency to conventional nerve conduction studies for the evaluation of sensitive nerve conduction parameters in type 2 diabetic patients with sensorimotor polyneuropathy

Short title: Arjun Baidya et al., Diagnostic accuracy of minimum F-wave latency and sural radial amplitude ratio (SRAR) to that of traditional NCS

Corresponding author:
Dr. Arjun Baidya, Associate Professor
Department of Endocrinology, Nil Ratan Sircar Medical College and Hospital, Kolkata, India
e-mail: drarjun.baidya@rediffmail.com

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ABSTRACT

Introduction: Measurement instruments used to evaluate neuropathy include several questionnaires, Biothesiometry, monofilament testing, and nerve conduction studies (NCS), the gold standard test. The purpose of this research is to develop a straightforward diagnostic procedure for the early diagnosis of diabetic peripheral neuropathy (DPN) by comparing the diagnostic accuracy of minimum F-wave latency and sural Radial Amplitude Ratio (SRAR) to that of traditional NCS.

Material and methods: This was a cross-sectional observational research conducted on 82 patients. Every patient had type 2 diabetes, with an average of 5.95 ± 4.85 years of diabetic control. The patients were then split into three groups: those with an HbA1c of less than 7.5%, those with an HbA1c of between 7.5 and 8.5%, and those with a HbA1c of more than 8.5%. Research on the nerve conduction of the tibial, Peroneal, sural, superficial radial, median, and ulnar nerves was included. The nerves were stimulated with supramaximum intensity 0.1 ms electric pulses in order to produce the highest possible amplitude of sensory nerve action potentials (SNAPs) and CMAPs. P-values < 0.05 were considered significant.
Results: When comparing the motor conduction velocity (MCV) of the ulnar, tibial, and median nerves to their respective F-wave latencies, the Z-score for CMAP amplitude was higher in all four motor nerves. In all four motor nerves, there was a significant relationship between MCV and the Z scores for low F-wave delay. Abnormal minimum F-wave latencies were seen in 69, 58, 18, and 22% of the nerves with normal MCV (the median, ulnar, tibial, and Peroneal nerves, respectively). Regular nerve conduction data showed that all groups showed a pattern of solely sensory involvement with a notable decrease in SNAP amplitudes but no change in nerve conduction velocities.
Conclusions: Electrophysiologic investigations of diabetic polyneuropathy should take into account minimal F-wave delay and the ratio between the amplitudes of the sural and superficial radial sensory nerve action potentials. These are sensitive markers for the diagnosis of nerve damage.
Keywords: polyneuropathies, type 2 diabetes, diabetic peripheral neuropathy, F-wave, sural radial amplitude ratio, nerve conduction studies

Introduction

Demyelinating sensory peripheral neuropathy and axonal degeneration occur simultaneously in diabetic polyneuropathy. Since nerve conduction tests are thought to be the most sensitive, dependable, noninvasive, and objective method for examining this condition, they are often employed to measure delay and velocity [1–4].

The three main categories of these peripheral sensory diseases are sensory neuronopathies (SN), sensory polyneuropathies (SP), and sensory multineuropathies (SM). Deficits that are symmetrical and dependent on length are often seen in sensory polyneuropathies. They are often linked to hereditary or systemic diseases like transthyretin familial amyloid polyneuropathy (ATTR-FAP) or diabetes [5]. On the other hand, sensory

mononeuropathy multiplex, or multifocal involvement of sensory nerves, is a characteristic of SM. Patients may have asymmetrical regions of hypoesthesia, with the arms often being more impacted than the legs. The neuropathy associated with leprosy, which is widespread in several parts of the globe, is an amazing example of SM [6]. Lastly, dorsal root ganglia injury in SN results in asymmetric sensory impairments and sensory ataxia [7]. However, depending on the course of the illness and its underlying cause, SN may sometimes manifest with broad and somewhat symmetric impairments (genetic subtypes of SN, such as Friedreich ataxia, Machado-Joseph disease, and RFC1-related illnesses, are commonly symmetric indeed) [8–10].

In most cases, a diagnosis may be made using standard nerve conduction testing when there are moderate to severe symptoms. However, electrodiagnostic diagnosis may provide a greater challenge in some individuals exhibiting milder symptoms. The majority of symptoms and clinical impairments of diabetic polyneuropathy are thought to be caused by axonal loss, which is marked by a distal to proximal gradient of severity, with the longest nerves in the lower limbs being impacted sooner than the nerves in the upper extremities [11–13]. As a result, one may expect an early decrease in the sural amplitude in comparison to the radial. Clinically, sensory complaints are a common complaint among diabetic polyneuropathy patients. It is thought that diabetic polyneuropathy mostly affects the distal nerve segments, and that sensory nerve conduction — particularly that of the sural nerve — is more compromised than that of the motor nerves [14]. F-wave tests have thus been deemed to be of little use in individuals with subclinical diabetic neuropathy [15]. F-wave measurements in diabetes patients, however, have reportedly been shown to be quite accurate lately [16]. Consequently, additional conventional nerve conduction measures including motor nerve conduction velocity (MCV), amplitude of compound muscle action potentials (CMAP), and distal latency (DL) were evaluated to assess the diagnostic sensitivity of the lowest F-wave delay. Additionally, it was looked into whether or not minimum F-wave delay and a straightforward ratio of the radial to sural sensory response amplitudes (SRAR) might be used to diagnose individuals with diabetic neuropathy electrodiagnostically.

Material and methods

Patients

The Institutional Review Board and Ethical Committee approved this cross-sectional observational research, which was carried out at a tertiary care teaching hospital (No: KPCMCH/IEC/470). Following informed permission, 82 diagnosed as T2DM (with a

haemoglobin A1c (HbA1c) ≥ 6.5 %, a fasting glucose ≥ 110 mg/dL, or a postprandial glucose ≥ 140 mg/dL despite appropriate diet and exercise, oral antihyperglycemic agents, or insulin therapy) patients between the ages of 30 and 65 were included to the research. A thorough neurologic examination of the upper and lower limbs was performed on each subject. At least two of the following conditions have to be met by the patients: symptoms of dysesthesia or parenthesis; decreased vibratory feeling below the knee; decreased ankle jerk in comparison to knee jerk; and decreased light touch and discriminating sense further down the legs. Exclusions from the study included patients with type 1 diabetes, lumbosacral radiculopathy, lumbar canal stenosis, ulcers, amputations, Charcot foot, obesity, cardiac pacemakers, rhythm abnormalities, and other diseases that impair peripheral nerve function, such as chronic liver and kidney disease, alcoholism and malnutrition. Since the early detection of diabetic peripheral neuropathy was the main goal of this research, patients with ulcers, amputations, and Charcot's foot were excluded. Following the exclusion of these people, 82 patients (27 men and 55 women, ages 52.09 ± 7.8 years) were eligible for this investigation. Every patient had type 2 diabetes, with an average of 5.95 ± 4.85 years of diabetic control. The patients were then split into three groups: those with an HbA1c of less than 7.5%, those with an HbA1c of between 7.5 and 8.5%, and those with a HbA1c of more than 8.5%. The proportion of individuals with cardiovascular and other problems rose with every 1% increase in HbA1c [17, 18].

Nerve conduction studies

Research on the nerve conduction of the tibial, Peroneal, sural, superficial radial, median, and ulnar nerves was included. Using the standardised method developed by Ma and Liveson [19], surface recordings were used in all investigations. The nerves were stimulated with supramaximum intensity 0.1 ms electric pulses in order to produce the highest possible amplitude of sensory nerve action potentials (SNAPs) and CMAPs. Both the lower and upper extremities' temperatures were equalised and kept between 31 and 34°C. Twenty stimuli were presented at a frequency of 1/s for the F response. After removing erroneous voluntary activity, Am F-wave was defined as an action potential with an amplitude of more than 20 μV and latency within a suitable range for the nerve under investigation. For every trace, the latency to the first deviation from the baseline was measured; the shortest delay, known as the minimum F-wave latency, was found. All stimulation of the sural and superficial radial nerves was done 10 cm proximally along the radius and 13 cm proximally in the mid-calf, respectively, in order to compare their amplitudes. Furthermore, a plastic bar containing a

disc electrode was used to maintain a consistent spacing between the reference and active electrodes.

Statistical analysis

Z scores [Z- (result value-age and height matched normal mean valued)/standard deviation] were used to represent the findings of motor nerve conduction tests using age and height matched normal mean value and standard deviation [19, 20]. The amplitude of CMAP, MCV, and minimum F-wave delay were the conduction parameters that were compared using paired student t-tests with the Bonferroni-corrected limit of significance. To compare the minimum F-wave delay data, the Z-score of the conduction velocities and response amplitudes was multiplied by –1. The Pearson product-moment correlations were used to determine the associations between the different parameters. By dividing the maximum sural amplitude by the highest radial amplitude found, the sural/radial amplitude ratios (SRAR) were computed. Neurophysiological data was shown to have a non-normal distribution ($p < 0.05$) using the Pearson correlation test. Descriptive statistics were used to display clinical, demographic, and fundamental NCS data. The Kruskal-Wallis test was used to assess the persistence and minimum and mean F-wave latencies and a posthoc Bonferroni analysis was conducted thereafter. The authors created receiver operator characteristic (ROC) curves for the parameters that may distinguish between the groups in order to calculate the area under the curve (AUC). P-values less than 0.05 after Bonferroni correction were deemed significant.

Results

82 patients in all were enlisted. Table 1 describes the baseline characteristics. The mean average duration of diabetes was 52.09 ± 7.8 years.

Table 2 displays the findings from the motor nerve conduction investigations, which include F-wave. In all four motor nerves, the Z-score for the amplitude of the CMAP was greater for the lowest F-wave latency than for the MCV of the ulnar, tibial, and median nerves (Table 2). In all four motor nerves, there was a significant relationship between MCV and the Z scores for low F-wave delay. The correlation coefficients for the median, ulnar, tibial, and peroneal nerves were, respectively, $\square = –0.41$ ($p < 0.05$), $\square = –0.66$ ($p < 0.01$), $\square = –0.76$ ($p < 0.01$), and $\square = –0.69$ ($p < 0.01$). When considering low F-wave delay, the number of aberrant nerves (Z score > 2 or < 2) was higher than the MCV and the amplitude of the CMAP of all four nerves.

Abnormal minimum F-wave latencies were seen in 69, 58, 18, and 22% of the nerves with normal MCV (the median, ulnar, tibial, and Peroneal nerves, respectively). In contrast, aberrant MCVs were found in 23, 0, 0, and 11% of the nerves (median, ulnar, tibial, and Peroneal nerve, respectively) with normal minimum F-wave delay (Table 3).

Table 4 displays the distribution of abnormal amplitudes on sensory nerve conduction investigations. Regular nerve conduction data (Table 4) showed that all groups showed a pattern of solely sensory involvement with a notable decrease in SNAP amplitudes but no change in nerve conduction velocities. All of these results point to an axonal pattern of sensory fibre involvement. Abnormalities in sensory nerve action potentials were asymmetric in the other groups, but symmetric in the HbA1c ≤ 7.5 group and limited to the lower limbs (particularly obvious in the sural and ulnar nerves).

84% of the patients with aberrant results in the conventional sensory nerve conduction testing had SRARs of less than 0.5, and their SRARs were substantially lower (0.31 ± 0.42) ($p < 0.05$). Furthermore, in the standard sensory nerve conduction testing, 50% of the participants exhibiting normal results had an SRAR of less than 0.5. An SRAR of less than 0.5 was seen in 67% of individuals exhibiting polyneuropathic symptoms overall (Table 5).

Discussion

This investigation discovered that the least F-wave latency, as opposed to either MCV or the amplitude of motor nerves in the upper and lower limbs, was a more sensitive indicator of aberrant nerve conduction in individuals with diabetic neuropathy. Furthermore, in 84% of patients with aberrant standard sensory nerve conduction testing results, the sural/radial amplitude ratio was less than 0.5. Furthermore, if the patient’s standard sensory nerve conduction result was aberrant, their ratio was much lower.

The Z scores for the minimum F-wave delay were considerably bigger than the MCV scores for the tibial, median, ulnar, and peroneal motor nerves. This finding may not always be connected to more severe pathological alterations along the motor nerve’s proximal segments. It can be the outcome of underlying methodological issues.

The F-wave has mostly been used to evaluate the function of the proximal portion of the motor nerves in the majority of earlier electrophysiological investigations of diabetes patients [19, 20]. There have been contradictory outcomes, nevertheless.

While some writers have observed that there is no difference between the proximal and distal regions, others have discovered that the MCV is slightly but noticeably more pronouncedly reduced in the distal parts [21]. The increased minimum F-wave delay might be

explained by a decrease in excitability of the anterior horn cells, a fall in conduction velocity, or a selective loss of the faster axon. Every motor neurone elects an F-wave 1–5% of the time after stimulation, therefore patients with reduced excitability will choose even fewer F-waves. Therefore, one may argue that 20 stimuli are inadequate to produce a representative population of F-waves, which could lead to a false positive of increased delay. However, Fisher discovered that when 10 stimuli were administered, the minimum F-wave latency was within 95% of the genuine minimal latency [23]. Since the minimum F-wave latency value in the present research is highly connected with the MCV value, it suggests that changes in conduction velocity are the primary cause of the increased minimal F-wave delay.

Minimal F-wave latency is another NCS criterion that is helpful in the subclinical diagnosis of peripheral neuropathy; its sensitivity and specificity were 78.6% and 76.5%, respectively. Comparable results of 78.6% and 63% for tibial F-wave latency and 74% and 70% for peroneal F-wave latency were reported by Weisman et al. [24].

Amplitude measures have been suggested as a useful tool for diabetic polyneuropathy clinical studies in recent years. This is because they more closely resemble axonal loss, the pathological modification that causes motor and sensory abnormalities in diabetic polyneuropathy [25]. The results of this research suggest that the pathophysiology of the axons may be largely intact since the Z-scores of the CAMP amplitude were less than those of the MCV and minimum F-wave delay. However, because of the wide range of reference amplitude values, Z-scores are comparatively modest, and as a consequence, the amplitude of CMAP is considered an insensitive metric when it comes to identifying problems in specific individuals.

About 50% of diabetic individuals with subclinical neuropathy have aberrant conduction velocity or SNAP amplitude [26]. Additionally, although every patient in the research had clinical indications of polyneuropathy, only 42 individuals (51%) in this study had impaired standard sensory nerve conduction. According to Seward et al., a critical ratio of less than 0.4 has a 90% specificity and a 90% sensitivity for the sural/radial amplitude ratio (SRAR), which is a sensitive and specific electrodiagnostic test for moderate polyneuropathy [27]. The distant degeneration of neurons is a hallmark of polyneuropathy [28–30], with the longest axons usually being impacted first. Since the longest nerve in the arm is the last to become impacted by the progressive proximal extension of degeneration, testing the SRAR may help identify polyneuropathy in diabetes patients, as shown by these earlier investigations. In the present investigation, SRAR was considerably lower ($p < 0.05$) in participants exhibiting aberrant findings in typical sensory nerve conduction, with 84% of

them having an SRAR of less than 0.5. Furthermore, an SRAR of less than 0.5 was seen in 50% of the participants exhibiting normal results in a typical sensory nerve conduction testing.

Group I's median nerves' left minimum and mean F-wave latencies were longer than those of Groups II and III. The most likely reason for this result was the high rate of carpal tunnel syndrome in this subgroup, which was seen in the analysis after the patient was taken out of the CTS. The three groups could not be stratified using any of the remaining F-wave latency data in any of the other nerves. The negative findings cannot be attributed to these confounding factors since the age and height of each of the three groups were matched. The axonal substrate was present in all three groups (I, II, and III), despite the varying lesion topographies within the PNS. Therefore, it is not shocking that the latencies were comparable among the groups.

While the present research focused on evaluating F-waves, some significant results were seen for other neurophysiological parameters. In fact, compared to Gr III, motor nerve conduction vectors in the arms were much lower in Gr I and Gr II. This suggests that even in cases where the clinical presentation is solely sensory, the former two groups have mild motor NC symptoms. On the other hand, since damage is limited to the dorsal root ganglia, clinical and NCS motor functions are basically unaffected in people with higher HbA1c levels. A further plausible rationale for the deceleration in motor nerve conduction velocity (NCV) pertains to the causes of the HbA1c level.

There are a few drawbacks to using SRAR as a test for diabetic polyneuropathy, however. Firstly, any modest isolated neuropathy of either nerve might alter the ratio since the SRAR depends on two different nerves being investigated. Moreover, individuals with diabetes who have major demyelinating components to their polyneuropathy may also have a skewed ratio. Patients with acute and chronic inflammatory demyelinating polyneuropathy showed a relative sparing of the sural sensory response amplitude in comparison to the median nerve [31]. Ultimately, obtaining an exact ratio depends on the technical accuracy with which each of the sensory reactions is recorded. Multiple efforts were made to maximise the response amplitude in each participant. In actuality, there is a clear association between ageing and a diminishing amplitude of the sural nerve. The authors of a previous study, however, proposed that rather than being a purely length-dependent process, the reductions in sensory amplitude with ageing were partly caused by nerve cell loss, most likely at the level of the dorsal root ganglion [32–34]. This study also revealed that the SRAR had no discernible correlation with age.

Limitations

Some potential drawbacks of the research include its cross-sectional design, small sample size, and failure to account for tiny fibre neuropathy. Normal NCS is affected significantly by age and height, which was not taken into consideration. A larger study with follow-up to observe the development of ulcers would give a more accurate sensitivity and specificity of the various tools.

Conclusion

Low F-wave delay is a more sensitive metric than both the amplitude of the Porter nerve and the conduction velocity of motor nerve fibres for identifying polyneuropathy in diabetes individuals. Consequently, F-wave analyses have to be a standard component of diabetes patient electrophysiological examinations. Furthermore, a sural/radial amplitude ratio has to be taken into account as an extra sensory nerve conduction investigation. The straightforward test may be especially helpful for patients with suspected polyneuropathy in whom the sural amplitude response is not clearly diagnostic.

Article information

Conflicts of interest: *There are no conflicts of interest.*

Declaration of patient consent: *The author attests that he has all necessary patient permission paperwork in his possession. The patient(s) has consented in writing to the publication of his or her photos and other clinical data in the journal. The patients are aware that while every attempt will be made to hide their identity and that their names and initials will not be published, anonymity cannot be guaranteed.*

Ethical approval: *This study was conducted in accordance with the Declaration of Helsinki, and approval for the study protocol was granted by the Ethics Review Board of KPC Medical College and Hospital. Participants and their parents were informed of their written consent before involving them in the study. Human rights were kept safe throughout the study.*

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Data availability: *The datasets generated and analyzed during the current study are available to the corresponding author upon reasonable request.*

Author contributions: *Arjun Baidya: conceptualization; formal analysis; methodology; writing — original draft; data collection. Mridul Bera: investigation; resources; formal analysis; data collection. Rishad Ahmed: conceptualization; supervision; data collection, writing — review and editing.*

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Table 1. Demographic data of all patients included in the study

Characteristic	**Total (n = 82)**	**Group I HbA1c ≤ 7.5% (n = 27)**	**Group II HbA1c > 7.5% but < 8.5% (n = 33)**	**Group III HbA1c ≥ 8.5% (n = 22)**	**Group comparison (Kruskal Wallis p-value)**
Age (years)	52.09 ± 7.8	51.38 ± 7.2	52.14 ± 7.6	53.02 ± 8.4	0.512
BMI [kg/m$^{2]}$	24.94 ± 2.91	24.26 ± 2.87	25.03 ± 2.92	24.78 ± 2.90	0.390
Duration of diabetes (years)	5.95 ± 4.85	5.5 ± 4.05	6.25 ± 5.01	5.93 ± 4.80	0.209
Sensory ataxia	54 (65.85%)	16 (29.62%)	26 (48.14%)	12 (22.24%)	< 0.001 ▲●
Paresthesia/hypoesthesia	47 (57.31%)	17 (36.17%)	21 (44.68%)	9 (19.14%)	< 0.001▶●

Neuropathic pain	65 (79.26%)	19 (29.23%)	29 (44.61%)	17 (26.15%)	0.120

BMI — basal metabolic rate; HbA1c — glycated haemoglobin; Notes: ▶ — Gr I × Gr II; ▲ — Gr 1 × Gr III; ● — Gr II × Gr III. Results are stratified for each diagnostic group

Table 2. Z scores for the amplitude of motor nerve conduct studies

Z-Scores	**Nerve**			
	Median	**Ulnar**	**Tibial**	**Peroneal**
F-lat	2.31 ± 1.34	2.02 ± 1.19	2.31 ± 1.21	2.34 ± 1.27
MCV	0.71 ± 1.36	1.13 ± 1.31*	1.72 ± 1.23*	2.02 ± 1.38
MAMP	0.05 ± 0.92*	–0.11 ± 0.84	0.64 ± 0.74*	0.58 ± 0.89*
DL	1.39 ± 3.79	0.05 ± 1.09*	0.65 ± 0.99*	0.03 ± 1.43*

*p < 0.05. For the composition of F-lat, the Z scores of MCV and MAMP were multiplied by –1

Asterisk means a significant difference between the Z-score of F-lat and that of MCV, MAMP, and DL in each nerve

Table 3. The frequency of normal results compared to aberrant findings in the motor nerves of the median, ulnar, tibial and Peroneal motor nerve

Nerve	**Abnormal MCV Normal F-Lat**	**Abnormal F-Lat Normal MCV**
Median	23 (9)	69 (22)
Ulnar	0 (8)	58 (17)
Tibial	0 (16)	18 (19)
Peroneal	11 (19)	22 (18)

The number of patients with abnormal findings is given for each nerve in parenthesis. NF, there was no abnormal finding. Normal: –2 ≤ Z score ≤ 2. Abnormal: Z score > 2 or < 3.

Table 4. Distribution of abnormal amplitudes on sensory nerve conduction studies

Nerve	**HbA1c ≤ 7.5% (n = 27)**	**HbA1c > 7.5% but < 8.5% (n = 33)**	**HbA1c ≥ 8.5% (n = 22)**	**Group comparison (Kruskal–Wallis p-value)**

Ulnar, (left/right)	66%/77%	56%/52 %	100%/100%	0.001▲● / < 0.001▲●
Median, (left/right)	72%/81%	48%/42 %	100%/100%	< 0.001▲● / < 0.001▲●
Radial, (left/right)	39%/67%	46%/64 %	61%/52%	< 0.001▲● / 0.003▲●
Sural, (left/right)	76%/82%	81%/79 %	61%/57%	0.263/0.026●
Superficial peroneal, (left/right)	79%/91%	81%/91 %	56%/78%	0.065/0.636

HbA1c — glycated haemoglobin; Notes: ▶ — Gr I × Gr II; ▲— Gr 1 × Gr III; ● — Gr II × Gr III

Table 5. Relationship between the standard sensory nerve conduction study and the sural/radial amplitude ratio

Standard sensory nerve conduction study	**Sural/radial amplitude ratio (No. of patients)**		**Mean ± SD**
	< 0.5 (%)	**≥ 0.5 (%)**	
Normal (n = 40)	19 (23)	21 (26)	0.59 ± 0.24
Abnormal (n = 42)	36 (44)	6 (7)	0.31 ± 0.42*
Total (n = 82)	55 (67)	27 (33)	

*p < 0.05