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Research Article

The Utility of a Novel Composite Parameter in Sensory Nerve Conduction Studies: Amplitude/ Rise Time of Sensory Nerve Action Potential

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Summary

Objective: To evaluate the new composite parameter (i.e., the ratio of amplitude to rise time) of sensory nerve action potential in patients with diabetic distal symmetric sensory polyneuropathy (DSSP).
Methods: 82 diabetic patients (two subgroups of normal and deteriorated NCS) and 34 controls were evaluated based on nerve conduction studies (NCS), rise time and the ratio of amplitude to rise time (A/RT).
Results: The A/RT (cut off value = 1) of medial plantar, sural (SU) and superficial peroneal nerves were quite informative in each group (P < 0.0001, for relevant nerves). However, SU-A/RT was more reliable and useful than other nerves based on specifity and predictive values.
Conclusions: Evaluation of SU-A/RT as an additional parameter would increase the diagnostic utility of NCS in detecting DSSP.

Key words: Distal symmetric sensory polyneuropathy, sensory nerve action potential, sural nerve

Duyusal Sinir ileti Çalışmalarında Yeni Bir Bileşik Parametrenin Kullanımı: Duyusal Sinir Aksiyon Potansiyelinde Amplitüd/ Yükselme Zamanı

Özet

Amaç: Diyabetik distal simetrik duyusal polinöropatili (DSDP) hastalarda duyusal sinir aksiyon potansiyelini yeni bileşik bir parametre (amplitüdün yükselme zamanına oranı) ile değerlendirmek.
Materyal ve Metod: 82 diyabetik hasta (elektrofizyolojik olarak normal ve hasarlı olarak iki alt grup) ve 34 kontrol sinir iletim çalışmaları (SİÇ), yükselme zamanı ve amplitüdün yükselme zamanına oranı (A/YZ) ile değerlendirildi.
Sonuçlar: Medial plantar, sural (SU) ve yüzeyel peroneal sinirler için A/YZ (ayrım değeri = 1) her iki hasta grubu için de oldukça bilgi vericiydi (P < 0.0001, sözü edilen sinirler için). Bununla beraber, özgüllük ve öngörüsel değerler göz önüne alındıklarında SU- A/YZ diğer sinirlere göre daha güvenilir ve kullanışlıydı.
Yorumlar: SU-A/YZ in ek bir parametre olarak değerlendirilmesi DSDP' nin araştırılmasında SİÇ nın tanısal kullanılabilirliğini artıracaktır.

Anahtar Kelimeler: Distal simetrik duyusal polinöopati, duyusal sinir aksiyon potansiyeli, sural sinir

INTRODUCTION

Distal symmetrical sensory polyneuropathy (DSSP) is the most prominent complication of diabetes with common features of length related, symmetric pattern of sensory loss. Sensory neuropathy usually begins at the most distal parts of extremities and extends proximally in time(15). Among the diagnostic tools, conventional nerve conduction study (NCS) is the main method in the diagnosis of neuropathy. Underestimation of the DSSP is always possible when the sensory NCSs are restricted to sural nerves as it is regularly done in most of the neurophysiology laboratories. However, assessment of the uncommon studied, distally located sensory nerves usually helps the clinician to determine the condition earlier(3,5,14).

However, the clinician has to face the problem of interpreting the data in the uncommon sensory NCS, i.e., evaluating in all or none [absence of sensory nerve action potential (SNAP)] fashion or taking the changes in amplitude, latency or velocity of SNAP into account. Also, it is not easy to agree on the lower limits of normative values, since sex and age may have influence on the SNAP parameters (i.e., latency, amplitude and velocity) of uncommon nerves. Above all, technical difficulties for obtaining SNAPs (i.e., distal entrapments, difficult localizations and patient discomfort) of uncommon nerves may force the clinician to be sure of not making a technical error. Therefore, usual SNAP parameters may be insufficient to evaluate subtle SNAP changes in uncommon nerve conduction studies. Also, commonly used parameters (latency, amplitude, NCV) and the rise time are influenced by common factors such as type of the nerve, type of degeneration, histological and anatomical properties, i.e.; nerve fiber diameter and length, skin thickness, stimulation intensity and the distance of stimulation to the nerve. It is possible to overwhelm these common influences via taking the ratio of one parameter (i.e.,amplitude) to another (i.e., rise time). Besides, an obvious change in SNAP morphology could be observed in either type of denervation process (i.e., reduction in amplitude due to axonal denervation or dispersion of SNAP duration due to demyelinating process). Therefore, the novel parameter (A/RT) would not only inform the clinician about the deterioration in the shape of the SNAP due to polyneuropathy which can be interpreted as a numerical value, but also would eliminate the common factors that would interfere on both amplitude and rise time. An increased sensitivity can be expected by evaluating such a parameter in detecting the patients with subtle electrophysiological changes due to neuropathy.

In this study, we aimed to get more information from the SNAPs by using the routine ENMG techniques at different stages of the diabetic DSSP. We tried to evaluate the morphological characteristics of SNAP, i.e., baseline to peak amplitude, the rise time and a new parameter that was obtained from the ratio of the amplitude to the rise time after converting them into millimeters (mm). The new parameter (i.e., A/RT) was expected to shorten the time needed for NCS by avoiding the use of uncommon NCS and overwhelm the difficulties that were mentioned above. Its utility was presumed to stand on the vulnerability of its components (i.e., rise time and amplitude) to the changes due to both axonal loss and/or segmental demyelination in diabetic DSSP process.

MATERIAL AND METHODS

Patients

Eighty two consecutive diabetic patients [40 males and 42 females; age between 34-84 years (mean age 57.34 ± 11.29 years)] with clinical diagnosis of DSSP were evaluated.

They had signs and symptoms of DSSP consisting of both small fiber sensory (i.e., pain and temperature sensation) and/or large fiber sensory (i.e., vibration and position sensation) functions.

In order to evaluate the patients regarding different severity levels of DSSP, the patients were recruited into the study and then classified into two sub-groups based on the limits of our laboratory. The cut off values for relevant nerves in our laboratory are as follows:

Medial plantar (MP) nerve; latency: 2.0 ms; amplitude: 3.5 mV, NCV: 38 m/s
Dorsal sural (DS) nerve; latency: 1.8 ms; amplitude: 3.0 mV, NCV: 35 m/s
Sural (SU) nerve; latency: 2.5 ms; amplitude: 6 mV, NCV: 40 m/s
Superficial peroneal (SP) nerve; latency: 2.5 ms; amplitude: 5.5 mV, NCV: 40 m/s
Radial sensory (Rd) nerve; latency: 1.9 ms; amplitude: 10 mV, NCV: 45 m/s
Ulnar sensory (Ul) nerve; latency: 2.5 ms; amplitude: 15 mV, NCV: 45 m/s

Twenty eight [14 males and 14 females; age 40-83 (mean 55.00 ± 10.35)] of them had normal routine NCS according to the cut off values of our laboratory and these patients were evaluated as group 1. Fifty four [29 males and 25 females; age 38-80 years, mean (58.39 ± 11.58)] patients had abnormal NCS according to the cut off values of our laboratory and they formed the group 2.

Subjects with one or more of the following were determined to be excluded: absence of proprioceptive and vibration sensations at the ankles, any distal wasting and weakness, generalized areflexia and absence of SNAP in all the sensory nerves of lower extremities or any previously documented cause of DSSP other than diabetes(6) and central nervous system disease.

Controls
Normative values for NCS parameters were obtained from 34 control subjects (16 males and 18 females; age 33-78 [mean 55.38 ± 10.92]) without any previously documented causes of DSSP(6).

The study protocol was in accordance with the Helsinki declaration of human rights, and was approved by the local Ethics Committee. All patients and controls gave written informed consent to participate in the study.

3.1. Clinical and Laboratory Evaluation

All the patients were evaluated for age, sex, weight, body-mass index, history of hypertension, smoking, lipid profile, electrocardiogram, fasting plasma glucose, and history of diabetes at first degree relatives. Polycystic ovarian syndrome and history of gestational diabetes were noted since both diseases are common risk factors for diabetes for female cases(9,10). Laboratory investigations included complete blood count, fasting blood glucose, HbA1c level, renal and liver function tests, thyroid function tests, vitamin-B12 level, folic acid level, erythrocyte sedimentation rate, rheumatoid factor, anti nuclear antibody, and protein electrophoresis.

All the patients were fully investigated with routine physical, neurological, and autonomic examinations after being evaluated based on the Neuropathy Symptom Profile (NSP)(2) and Autonomic Symptom Profile (ASP)(12).

Neurological Examination
All the patients were fully examined by means of neurological examination and autonomic features i.e., evaluations for atrophic changes, heart rate and blood pressure. The examination included the Achilles tendon reflex, dorsiflexion strength of the hallux, distal pinprick perception at the dorsum of the hallux, vibration threshold, and fine touch sensation. Vibration sense was assessed with a 128-Hz tuning fork to the dorsum of the hallux. It was accepted as abnormal if the patient felt the vibration for 10 seconds or less. Fine touch was accepted normal if a 10-g monofilament was felt in least 9 of 10 tries when applied to the dorsum of the hallux.

Electrophysiological Evaluation
All electrophysiological data were recorded using a Medelec Synergy EMG machine (Carefusion Manufacturing, Galway, Ireland). Conventional surface electrode techniques were used in the NCS. Adding uncommon nerves such as medial

plantar and/or dorsal sural was shown to increase the sensitivity of the NCS to diagnose DSSP(3,5,14). Thus, sensory NCS was performed in bilateral SU, SP, DS and MP nerves in all of the patients' and controls' lower extremities.

In the upper extremities ulnar sensory, radial sensory conductions were studied unilaterally from the left arm. Median sensory nerve was not evaluated because of its high vulnerability to entrapment in the carpal tunnel. Except for the MP nerve, all sensory nerves were studied antidromically. An average of 8 trials was used in all sensory NCS. In order to obtain an optimal SNAP, the stimulus intensity was at least 3 times the sensory threshold. Filter settings were 20 Hz–2 kHz for sensory NCS, sweep duration was 20 ms and sensitivity was 20 µV for sensory studies. Skin temperature was controlled and maintained between 31 and 34°C in all subjects.

Motor NCS and F-waves was studied in bilateral posterior tibial and common peroneal nerves of all subjects but the data were out of this study's concern.

Evaluation of a SNAP

All of the SNAPs were evaluated according to the parameters of onset latency (the onset of the first negative deflection and it was used to calculate the conduction velocity), baseline to peak amplitude of the negative deflection of the potential (A), rise time (RT, i.e., the time interval between the beginning and the peak of SNAP), nerve conduction velocity (NCV, i.e., division of the difference of the distance between the cathodes of the stimulating point to the recording electrode to the onset latency of SNAP) and the ratio that was elicited by dividing the amplitude to the rise time (A/RT)after converting them into distances by means of mm.

The values of A and RT (Value-1 and Value-2,respectively) were converted into mm after placing the known variables (i.e. one horizontal division of 18mm corresponded to 2ms and one vertical division of 18mm corresponded to 20 µV) into following simple equations:

For amplitude; Value-1 (mm) x 20 (µV) = 18(mm) x A (µV)
For rise time; Value-2 (mm) x 2 (ms) = 18(mm) x RT (ms)

The composite parameter practically informs about the slope of the rising leg of the SNAP (i.e., if the ratio is "1", it would mean that the rise time is in the same magnitude with the base to peak amplitude (slope is 45°) (Fig 1A), "<1" with rise time is greater than the amplitude (slope is less than 45°) (Fig 1B), and ">1" with rise time is greater than the amplitude (slope is greater than 45°) (Fig 1C), by means of mm respectively.

The crucial point was obtaining the SNAP as precisely as possible. In order to measure the rise time and amplitudes accurately, we averaged the potentials for at least 20 times. Potentials with definite peak point formed by the ascending and the descending legs were easy to plot, but for SNAPs with broader peak, we plotted the highest point at the middle of the slope of the peak of SNAP peaks for determination of the rise time and amplitude (Fig 1D).

The rise time was preferred to the duration of SNAP for evaluation, since the ending point of the SNAP could be accepted as either the end of negative portion or the end of the total SNAP including the negative and positive components of the potential together.

Statistical analysis

SPSS for Windows 10.0 (SPSS Inc., Chicago, IL, USA) statistics programme was used for evaluation of data except for A/RT. Student's test, Mann Whitney-U test, Fisher exact test and Chi-square test were used for comparisons. The statistical significance limit was accepted as P <0.05.

The value "1" was accepted as the limit for evaluation of A/RT for practical purposes as mentioned in 3.4.

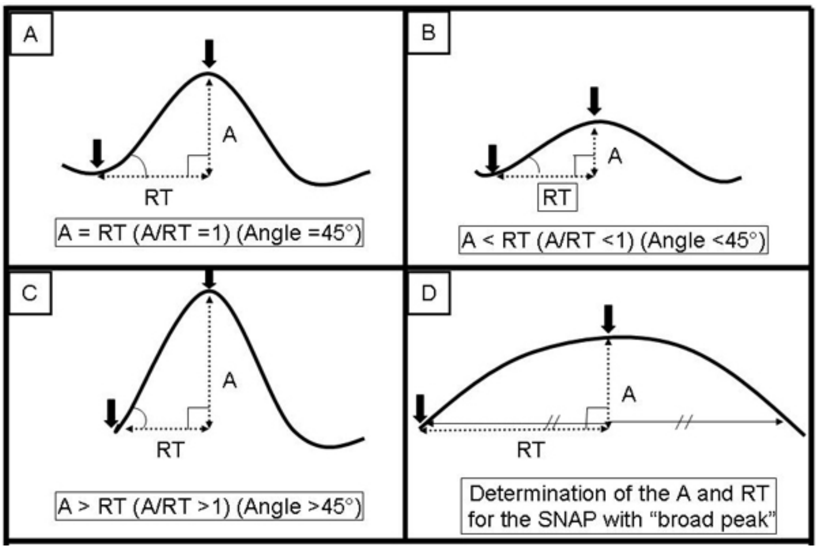

Figure 1: *Determination of the plotting targets (↓) of the beginning and the peak points for the evaluation of sensory nerve action potentials (SNAPs) with the parameters of amplitude (A), rise time (RT) and the angle of the hypotenuse that is formed after the settlement of A and RT to the corresponding sides of a right angled triangle in the SNAP, relative to baseline (reflects the ratio of A/RT after the A and RT were converted to mm as defined in methods section 3.4.). 1A, SNAP with A=RT; 1B, SNAP with A<RT; 1C, SNAP with A>RT; 1D, SNAP with a broad peak.*

RESULTS

Demographics and clinical parameters

There were no statistical differences between the patient groups and control subjects for age, gender, weight, height and body mass indices (P >0.05). All demographic parameters and clinical characteristics were demonstrated in Table 1.

Electrophysiological evaluation

SNAPs were obtained from all sensory nerves of the subjects in the first patient group. In group 2, SNAPs were not obtained from L-MP and R-MP, and L-DS nerves in 23 (41.5 %), from R-DS nerve in 21 (38.8 %) and from both-SU nerves in 2 (3.7 %) patients, respectively. SNAPs of SP nerve were obtained for left and right sides in the 46 (85.1%) and 48 patients (88.8%), respectively. Rd- and Ul- SNAPs were obtained in all patients.

Comparisons of the latency

Latencies did not show any significant difference between patient groups and controls. (P >0.05)

Comparisons of the NCV

There was no significant difference between control subjects and group 1 for NCV in any of the evaluated sensory nerve (P>0.05, for all comparisons). On the other hand, there was significant slowing in all nerves of group 2 patients when compared with group 1 patients and controls (P < 0.05). Assessment of NCV was able to define only 1(3.6%) subject in group1 and ten (18.5%) subjects in group 2 (Table 2).

Comparisons of the rise time

Neither of the nerves showed significant differences when compared between the patient groups and the controls (P >0.05).

Comparisons of the Amplitudes

There was no obvious change for amplitudes between group1 and control subjects (P >0.05).

Group 2 had significantly reduced amplitudes when compared with controls and group 1 (P < 0.05) (Table 3). Nevertheless, assessment of amplitudes was able to define the DSSP in 6 (11.5%) patients of this group (Table 3).

Comparisons of the A/RT

There was no obvious change for A/RT between group 1 and controls (P >0.05) (Table 4).

Table 1. Demographics and clinical characteristics of the patient groups

Demographics	**Group 1** **(n=28)**	**Group 2** **(n=54)**
Age (years)	55.38± 1.92	58.39±11.58
Height (cm)	161.09±8.35	164.57±7.97
Body mass index (kg/m^2)	1.77± 0.47	1.84±0.66
HbA1c (mg/dl)	7.26 ± 0.85	7.72± 0.86
Time elapsed after the DM diagnosis	5.97±5.96	8.87±6.64
Clinical characteristics according to the number of subjects	**n (%)**	**n (%)**
Insulin	8 (28 %)	7 (12.9 %)
Oral antidiabetic drugs	20 (71.4 %)	36 (66.6 %)
Family history of diabetes	18 (64.2%)	28(51.8%)
Stocking hypoesthesia (hands normal)	25 (89%)	21 (38.8 %)
Stocking and gloving hypoesthesia	3 (10.7%)	8 (32 %)
Impairment of position sensation	0	5 (9.2%)
Vibration impairment at toes	1 (3.5%)	26 (48.1%)
Diminished ankle reflex	0	16 (29.6%)
Absent ankle reflex	0	0
Motor deficit	0	0

Table 2. Number and percentages of abnormal patients according to the ratio of sensorial NCV among groups

Sensory NCV	**Group 1**	**Group 2**	**Controls**	***P* *all groups***	***P* Gr1 vs Gr2**	***P* Gr1 vs Cnt**	***P* Gr2 vs Cnt**
L-MP (LNV: 43.25 m/s)	59.47±9.19	52,87±9,53	58.05±7.26	0.011	0.013	0.795	0.049
R-MP (LNV: 43.28 m/s)	57.97±8.36	51,98±8,61	62.36±8.69	0.008	0.016	0.966	0.022
L-DS (LNV: 28.92 m/s)	46.37±8.73	40,75±5,88	42.64±6.86	0.013	0.010	0.110	0.047
R-DS (LNV: 30.42 m/s)	46.57±7.79	40,32±8,00	42.57±6.46	0.018	0.016	0.554	0.043
L-SU (LNV: 34.07 m/s)	46.37±8.73	46,96±6,64	42.64±6.86	0.002	0.002	0.396	0.039
R-SU (LNV: 38.39 m/s)	51.71±8.15	4,53±6,43	48.99±5.30	<0.0001	<0.0001	0.242	0.050
L-SP (LNV: 37.07 m/s)	51.37±8.15	47,10±8,12	51.91±7.42	0.016	0.044	0.962	0.024
R-SP (LNV: 34.42 m/s)	50.96±6.39	47,00±8,65	50.60±8.09	0.055	0.012	0.983	0.018
L-RD (LNV: 48.09 m/s)	64.29±5.72	58,16±6,54	60.71±6.31	<0.0001	<0.0001	0.070	0.016
L-UL (LNV: 44.69 m/s)	53.59±4.19	50,64±6,06	53.79±4.55	0.009	0.048	0.989	0.019
Comparisons according to number of the subjects	**Group 1 n (%)**	**Group 2 n (%)**	**Controls**		***P* Gr1 vs Gr2**	***P* Gr1 vs Cnt**	***P* Gr2 vs Cnt**
L-MP	1 (3.6%)	5 (16,7%)	0 (0%)		0.195	0.452	0.019
R-MP	1 (3.6%)	5 (17,2%)	2 (5.9%)		0.194	-	0.233
L-DS	0 (0%)	1(3,3%)	0 (0%)		-		0.469
R-DS	0 (0%)	2 (6,5%)	0 (0%)		0.493		0.224
L-SU	0 (0%)	1(1,9%)	0 (0%)		-	0.498	0.559
R-SU	0 (0%)	5(9,6%)	0 (0%)		0.156		0.152
L-SP	0 (0%)	3(6,8%)	0 (0%)		0.277	-	0.628
R-SP	0 (0%)	2(4,2%)	0 (0%)		0.528		0.511
L-RD	0 (0%)	2(3,8%)	1 (2.9%)		0.542	-	-
L-UL	0 (0%)	10(18,5 %)	1 (2.9%)		0.026	0.369	0.045

NCV, nerve conduction velocity; LNV, lowest normal value according to normative values obtained from controls; m/s, meters per second; L-MP, left medial plantar; R-MP, right medial plantar; L-DS, left dorsal sural; R-DS; right dorsal sural; L-SU, left sural; R-SU, right sural; L-SP, left superficial peroneal; R-SP, right superficial peroneal; L-RD, left radial; L-UL, left ulnar; Cnt, controls

Table 3. Number and percentages of abnormal patients according to amplitudes among groups

Amplitudes	**Group 1**	**Group 2**	**Controls**	***P* *all groups***	***P* Gr1 vs Gr2**	***P* Gr1 vs Cnt**	***P* Gr2 vs Cnt**
L-MP (LNV: 0.04mV)	8.99±2.50	3,85± 2,68	9.72±4.84	<0.0001	<0.0001	0.769	<0.0001
R-MP (LNV: 0.3mV)	7.89±3.66	3,95± 2,04	9.64±4.67	<0.0001	<0.0001	0.158	<0.0001
L-DS (LNV: 0.15mV)	6.67±3.42	4,01± 2,27	6.77±3.31	0.001	0.005	0.992	0.002
R-DS (LNV: 0.21mV)	7.36±3.91	4,78± 2,85	6.75±3.27	0.009	0.011	0.757	0.051
L-SU (LNV: 4.27mV)	18.59±7.26	9,20± 4,74	16.53±6.13	<0.0001	<0.0001	0.362	<0.0001
R-SU (LNV: 3.18mV)	17.80±5.27	8,82± 4,32	17.00±6.91	<0.0001	<0.0001	0.835	<0.0001
L-SP (LNV: 0.2mV)	*8.54±3.79*	6,03± 3,35	10.32±5.06	<0.0001	0.036	0.211	<0.0001
R-SP (LNV: 3.07mV)	10.78±6.61	6,46± 3,12	10.97±3.95	<0.0001	<0.0001	0.985	<0.0001
L-RD (LNV: 6.72mV)	21.98±7.82	16,24± 6,12	22.84±8.06	<0.0001	0.002	0.884	<0.0001
L-UL (LNV: 0.51mV)	28.65±11.4	19,41± 10,2	28.11±13.8	<0.0001	0.003	0.983	0.003

Comparisons according to number of the subjects	**Group 1 n (%)**	**Group 2 n (%)**	**Controls**		***P* Gr1 vs Gr2**	***P* Gr1 vs Cnt**	***P* Gr2 vs Cnt**
L-MP	0 (0%)	0 (0%)	0 (0%)		-	-	-
R-MP	0 (0%)	0 (0%)	0 (0%)		-	-	-
L-DS	0 (0%)	0 (0%)	0 (0%)		-	-	-
R-DS	0 (0%)	0 (0%)	0 (0%)		-	-	-
L-SU	0 (0%)	6 (11.5%)	0 (0%)		0.089	-	0.077
R-SU	0 (0%)	5 (9.6%)	0 (0%)		0.156	-	0.152
L-SP	0 (0%)	0 (0%)	0 (0%)		-	-	-
R-SP	0 (0%)	0 (0%)	0 (0%)		-	-	-
L-RD	0 (0%)	3 (5,7%)	0 (0%)		0.548	-	0.277
L-UL	0 (0%)	0 (0%)	0 (0%)		-	-	-

LNV, lowest normal value according to normative values obtained from controls; L-MP, left medial plantar; R-MP, right medial plantar; L-DS, left dorsal sural; R-DS; right dorsal sural; L-SU, left sural; R-SU, right sural; L-SP, left superficial peroneal; R-SP, right superficial peroneal; L-RD, left radial; L-UL, left ulnar; Cnt, controls

Table 4. Number and percentages of abnormal patients according to A/RT among groups

A/RT*	Group 1	Group 2	Controls	*P* *all groups*	*P* Gr1 vs Gr2	*P* Gr1 vs Cnt	*P* Gr2 vs Cnt
L-MP	1.35±0.41	0.54± 0.43	1.45±1.00	<0.0001	<0.0001	0.966	<0.0001
R-MP	1.53±1.89	0.62± 0.45	2.94±9.45	<0.0001	<0.0001	0.828	<0.0001
L-DS	1.06±0.50	0.64± 0.63	0.97±0.42	0.007	0.008	0.758	0.039
R-DS	1.05±0.56	0.73± 0.45	1.03±0.53	0.031	0.035	0.989	0.049
L-SU	2.65±1.15	1,15± 0.59	2.34±0.85	<0.0001	<0.0001	0.050	<0.0001
R-SU	2.39±0.81	1,13± 0.55	2.41±1.10	<0.0001	<0.0001	0.994	<0.0001
L-SP	1.20±0.55	0.73± 0.39	1.85±1.74	<0.0001	0.005	0.151	<0.0001
R-SP	1.47±1.02	0.86± 0.44	1.48±0.61	<0.0001	0.001	1,000	<0.0001
L-RD	3.99±1.52	2,75± 1,19	3.82±1.55	<0.0001	0.001	0.883	0.002
L-UL	4.44±2.15	2,76± 1,49	4.09±1.95	<0.0001	<0.0001	0.737	0.003
Comparisons according to number of the subjects with A/RT<1	**Group 1 n (%)**	**Group 2 n (%)**	**Controls**		***P* Gr1 vs Gr2**	***P* Gr1 vs Cnt**	***P* Gr2 vs Cnt**
L-MP	5 (17.9%)	27 (90%)	10 (29.4%)		<0.0001	0.290	<0.0001
R-MP	6 (21.5 %)	25 (86.2%)	11 (32.4%)		<0.0001	0.394	<0.0001
L-DS	14 (50.0%)	25 (83.3%)	19 (55.9%)		0.007	0.644	0.018
R-DS	14 (50.0%)	24 (77.4%)	19 (55.9%)		0.028	0.644	0.067
L-SU	1 (3.7%)	24 (46.2%)	0 (0%)		<0.0001	0.443	<0.0001
R-SU	1 (3.7%)	22 (42.3%)	0 (0%)		<0.0001	0.452	<0.0001
L-SP	8 (29.6%)	34 (77.3%)	7 (20.6%)		<0.0001	0.415	<0.0001
R-SP	8 (29.6%)	33 (68.8%)	8 (24.2%)		0.001	0.639	<0.0001
L-RD	0 (0%)	3 (5.7 %)	0 (0%)		0.548	-	0.277
L-UL	0 (0%)	4 (7.4%)	0 (0%)		0.296	-	0.156

A/RT; ratio of amplitude to the rising time;*, Cut off value = ”1” for all nerves; L-MP, left medial plantar; R-MP, right medial plantar; L-DS, left dorsal sural; R-DS; right dorsal sural; L-SU, left sural; R-SU, right sural; L-SP, left superficial peroneal; R-SP, right superficial peroneal; L-RD, left radial; L-UL, left ulnar; Cnt. controls

Apart from the marked changes in DS and SP nerves (0.05< P <0.001), the SNAPs of the other nerves in lower extremities revealed very significant reduction in Group 2 when compared with Group 1 and controls (P < 0.0001, for both comparisons). SU- nerve was demonstrated as an example for the change in amplitude, rise time and angle (equivalent of A/RT after the components were converted into mm) for control (Fig 2A) and diabetic subjects in group1 (Fig 2B), group 2 (Fig 2C).

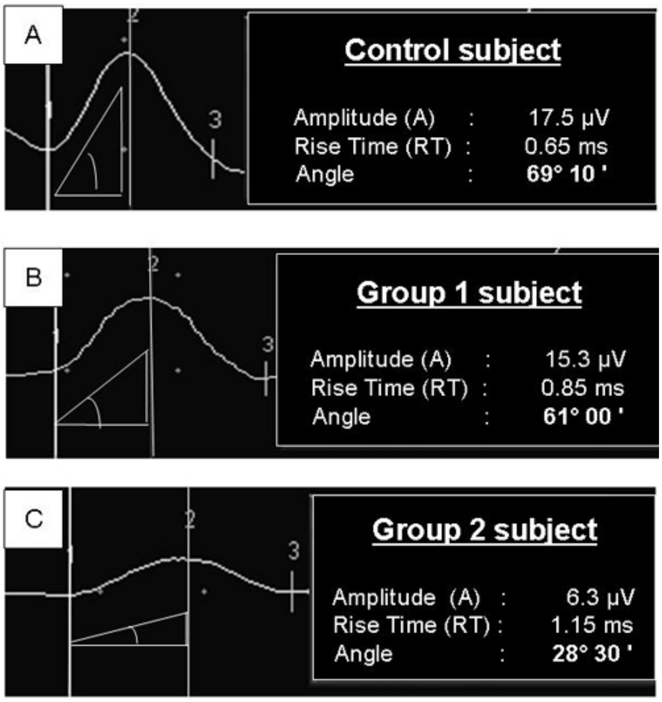

Figure 2: *The sural sensory nerve action potentials (SNAP) from control (2A) and patient groups 1 (2B) and 2 (2C). Sweep duration was 20 ms and sensitivity was 20 µV. The baseline to peak amplitudes and the rise times were converted to mm as was explained in "methods". After converting the data into mm, the first datum was divided to the second one in order to yield the A/RT. This composite parameter (A/RT) was practical in the patients of group 2, for the determination of the angle in the ascending leg of the SNAP relative to the baseline. Please notice that the A/RT was informative for defining the patient, however the amplitude was above the lower limit according to -2SD of the normative values (NV) (The lowest limit for NV in left sural nerve 4.27 mV and in right sural nerve 3.18 mV, respectively according to the -2SD).*

When the A/RT ratio cut off limit was accepted as "1", MP, SU and SP nerves were more informative for determining the patients in each group (P < 0.0001, for relevant nerves). MP and DS-nerves had higher sensitivities in defining the patients in both groups. However, SU-nerve was more reliable and useful for evaluation when specifity and predictive values were taken into account (Table 5). For example; Each DS- A/RT was able to define 50% and almost 80% of patients in group 1 and group 2, respectively; whereas its specifity was relatively low (29.4%). On the contrary, SU- A/RT was able to define DSSP in almost 45% of the patients in group 2, when compared to 1(1.8%) patient for latency, 0 (0%) for rise time, 6 (11.1%) for amplitude and 10 (18.5%) patients for NCS (Tables 2, 3 and 4). Although the sensitivity of A/RT was higher than other parameters (10.7% vs. 0 %, for latency, RT, A and NCV, respectively), it was unsatisfactory to diagnose the patients in Group 1 (Table 5).

Table 5. Diagnostic evaluation of A/RT in different nerves among patient groups

A/RT for Group1	Sensitivity %	Specifity %	Positive Predictive Value	Negative Predictive Value	Accuracy
MP*	46.4	50.0	43.3	53.1	48.4
DS*	64.3	29.4	42.9	50.0	45.1
SU*	10.7	100.0	100.0	57.6	59.6
SP*	46.4	58.8	48.1	57.1	53.3
RD*	-	-	-	-	-
UL*	-	-	-	-	-
A/RT for Group 2	**Sensitivity %**	**Specifity %**	**Positive Predictive Value**	**Negative Predictive Value**	**Accuracy**
MP*	94.4	50.0	75.0	85.0	77.3
DS*	94.4	29.4	68.0	76.9	69.4
SU*	55.6	100.0	100.0	58.6	76.1
SP*	87.0	52.8	77.0	74.1	72.7
RD*	7.4	100.0	100.0	40.5	43.1
UL*	7.4	100.0	100.0	40.5	43.1

A/RT; ratio of amplitude to the rising time; *, The values corresponding each nerve regardless of sides were determined after the data of both sides were evaluated to come from the normal distribution; MP, medial plantar; DS, dorsal sural; SU, sural; SP, superficial peroneal; RD, radial sensory nerve; UL, ulnar sensory nerve

DISCUSSION

In this study, we observed that the composite parameter of A/RT in SU nerves was able to define the patients in group 2 better than any other parameter i.e., latency, rise time, amplitude and NCV. By accepting the limit for A/RT as “1”, we were able to increase the diagnostic utility of the SU- NCS only by observing the slope of the ascending leg (arithmetically the ratio of amplitude to rise time after converting their magnitudes into mm) of the SNAP as discussed in methods. Unfortunately, this parameter defined a small number of the patients in group 1.

Sural nerve is the most common studied nerve of lower extremities in conventional sensorial NCS in the lower extremities. However SP-NCS was shown to be more vulnerable in DSSP and had a higher diagnostic value(7). Our results of low sensitivities for common parameters (i.e., latency, amplitude and NCV) for S and SP nerves even in patients with confirmed diabetic neuropathy questioned the utility of the NCS of these nerves, despite of their technical feasibilities.

MP and DS nerves are the two uncommon nerves that have been evaluated for the earlier diagnosis of diabetic polyneuropathy(3,5). However, MP-NCS can not only be uncomfortable for the patient, but also be affected due to local entrapment neuropathies. Thus, it is accepted to be insufficient for the evaluation of DSSN alone(8). On the other hand, assessment of the DS-NCS may recognize peripheral neuropathy at the early stages of the disease(5). Besides, entrapment of DS is very rare and its superficial location allows fine measurement of NCS(1,4). However, it is difficult to place the stimulator or the recording electrode under the lateral malleolus at optimum position and yield the accurate SNAP. Another distal nerve studied for the early detection of DSSN is the interdigital nerve(11). Despite of its introduction as a sensitive and objective in DSSN(11) it is uncomfortable and takes long time to evaluate all of its branches. Hence, it would be hard for the patient to be undergone and the clinician to perform such an extended electrodiagnostic procedure consisting of all of the nerves that were mentioned above. It could take approximately an hour and inevitably be bothersome both for the patient and the clinician to confirm or exclude the pre-diagnosis of DSSP.

In our study, the diagnosis of patients in Group 2 was confirmed based on those uncommon NCS. Nevertheless if the NCS in lower extremities was confined to SU-nerves as it is done in most laboratories, we would be able to define less than ten percent of the patients. In this point, SU-A/RT can help the electromyographer to decide on the extension or limitation of sensory NCS by means of uncommon nerves (i.e., MP, DS and interdigital nerves) in lower extremities. Our results showed that; A/RT was superior to other parameters for SU-nerve than the other nerves for evaluation. SU- A/RT was “less than 1” in almost half of Group, 2 but “more than1” in Group 1 and controls.

Regardless of the conventional NCS parameters (i.e., latency, amplitude and NCV) in normal ranges, the reduction in slope of the ascending leg of the SU-SNAP to less than 45° could be accepted as a red flag for NCS. This may help the clinician to make an assumption on the existence and severity of DSSP in the beginning of sensory NCS in lower extremities. Unfortunately, SU-A/RT was unsatisfactory to define the patients in group 1 and it would be necessary to assess the SNAPs of other nerves, if the SU-A/RT is >1. The higher capacity of the composite parameter (i.e., A/RT) would reflect the changes due to prolongation in rise time (which could be mentioned to be influenced by the demyelinating character of DSSP) or reduction in amplitude (which could be mentioned to be influenced by either the axonal loss or the demyelination or both pathopyhysiological processes of DSSP) or both, as reduction of A/RT ratio.

The underlying mechanism for reduction in A/RT could be explained by the anatomical deficiency of blood nerve barrier in the distal nerve terminals of distal sensory nerves. This deficiency makes them more vulnerable to both the axonal dying back degeneration and systemic inflammatory process which is also a core mechanism of DSSP in diabetes(13). Pathological data confirmed that segmental demyelination exists as well as axonal injury in diabetic DSSP. Main characteristic findings of diabetic polyneuropathy are axonal degeneration, regeneration and a lesser degroupee of secondary segmental demyelination(15). These findings are reflected to NCS as both reductions in amplitude, prolongation of SNAP latency and slowing of NCV. Segmental demyelination explains why slowing of conduction velocity is seen more than expected in predominantly axonal impairment of diabetic polyneuropathy. Moreover, remyelination process, structural abnormalities in paranodal ion channels, metabolic derangement at micromileu and subsequent propagation defects of action potentials may contribute to slowing of the action potential(15).

In our study, slowing of the NCV was found to be more evident as DSSP progressed, however this finding was not informative in defining the patients. Also, the rise time and latency was not informative because of the nerves' little variability in diameter and the thin myelin component individually. Reduction in amplitude was significantly higher in the distally located nerves than proximal located ones in patients of Group 2.

Relatively small size of Group 1 and controls was the most important limitation of this study. A / RT could be expected to define a higher amount of patients in Group 1 and a narrower range of limits for normative values of NCS parameters could be elicited, if number of subjects in those groups were higher. Also, neither of the parameters was able to define the patients in Group 1 precisely. Besides; although A/RT seems to be a bit stronger than commonly used NCS parameters (i.e., latency, amplitude and NCV) in detecting subtle deterioration in myelinated sensory nerves, advanced techniques evaluating the deterioration in un- or thinly- myelinated sensory nerves (i.e., laser evoked potentials, quantitative sensory testing, skin biopsy) are still better tools for verification of the DSSP pre-diagnosis in patients with normal NCS.

Diabetic neuropathy was a good model to evaluate the validity of A/RT in DSSP, but it can be assessed in other models such as entrapments or different neuropathic models as well. Also for the daily use, comparing the angle of the hypotenuse (ascending leg of the SNAP) that is formed after the settlement of A and RT to the corresponding sides of a right angled triangle in the SU-SNAP, would help the clinicians in electrophysiology laboratory (who are under heavy burden of high number of patients but less time for the electrodiagnostic procedure usually) to get valuable clues about the existence and severity of the DSSP.

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