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F-wave latency serves as the most reproducible measure in nerve conduction studies of diabetic polyneuropathy: multicentre analysis in healthy subjects and patients with diabetic polyneuropathy

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Abstract

Aims/hypothesis. For use in future drug development for diabetic polyneuropathy, we conducted multicentre trials to assess the reproducibility of nerve conduction studies.
Methods. All measurements were repeated twice at a time interval of 1–4 weeks in 132 healthy subjects (63 men) and 172 patients (99 men) with diabetic polyneuropathy. Using a standardised method, 32 centres participated in the study of control subjects and 65, in patients with diabetic polyneuropathy. Motor nerve conduction studies consisted of stimulating the left median and tibial nerves and recording the compound action potential from abductor policis and adductor hallucis for measuring amplitude, terminal latency and minimal F-wave latency. For sensory conduction studies, sensory nerve action potentials were recorded antidromically from the second digit and the posterior aspect of the lateral malleous after distal stimulation of the left median and sural nerves. We also calculated motor conduction velocity, F-wave conduction velocity and sensory conduction velocity. The relative intertrial variation and intraclass correlation coefficient were used as an index of reproducibility.
Results. Of all the measurements, F-wave latency yielded the highest intraclass correlation coefficient with the smallest relative intertrial variation for both median and tibial nerves in both groups.
Conclusion/interpretation. Median and tibial F-wave latency provide the most reproducible measures for a nerve conduction study, serving as one of the best measures in multicentre drug trials for diabetic polyneuropathies. [Diabetologia (2000) 43: 915–921]

Keywords Nerve conduction study, reproducibility, F-wave latency, diabetic polyneuropathy, serial study, drug trial, intraclass correlation coefficient (ICC), intertrial variation, nerve conduction velocity, sensory nerve action potential, motor conduction velocity.

Nerve conduction study is widely used for the assessment of diabetic polyneuropathy (DPN) not only to evaluate the degree of abnormality but also to document serial changes in the clinical course in general and drug effect in particular. Although the method provides us with a sensitive and objective indicator, its reproducibility primarily depends on the adherence to the widely accepted technical details. Any deviation from the standards results in inconsistent results. It is especially important to be aware of this in designing a multicentre clinical trial, with many investigators of different backgrounds and training. Few studies have tested the reproducibility of nerve conduction measurements in the evaluation of DPN [1–6]. We, therefore, conducted a multicentre study on intertrial variability and reliability in healthy sub-

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Abbreviations: DPN, Diabetic polyneuropathy; CMAP, compound action potential; TL, terminal latency; FWL, minimal F-wave latency; SNAP, sensory nerve action potentials; MCV, motor conduction velocity; FCV, F-wave conduction velocity; SCV, sensory conduction velocity; RIV, relative intertrial variation; ICC, intraclass correlation coefficient.

Table 1. The median value with 5th to 95th centile range of the measurements in healthy subjects and patients with DPN

	Healthy subjects			Patients with diabetic polyneuropathy		
	No.	Median value of 1st trial (5th–95th centile)	Median value of 2nd trial (5th–95th centile)	No.	Median value of 1st trial (5th–95th centile)	Median value of 2nd trial (5th–95th centile)
Median nerve, motor						
CMAP amplitude (wrist st.) (mV)	101	8.8 (4.1–13.0)	8.9 (4.4–13.2)			
TL (wrist to APB) (msec)	101	3.2 (2.6–4.0)	3.2 (2.6–4.0)	148	3.8 (2.9–5.6)	3.8 (2.9–5.7)
FWL (wrist st.) (msec)	90	24.6 (21.7–28.6)	24.9 (21.6–28.4)	147	27.6 (23.6–31.8)	27.6 (23.7–31.0)
MCV (wrist-elbow) (m/sec)	101	59.1 (51.6–68.1)	59.3 (51.6–65.9)			
FCV (wrist st.) (m/sec)	90	67.4 (57.8–75.5)	67.7 (58.7–76.0)	147	60.0 (51.4–70.0)	60.0 (51.0–68.6)
Tibial nerve, motor						
CMAP amplitude (ankle st.) (mV)	107	11.8 (6.0–21.3)	12.4 (5.5–21.1)	142	7.9 (3.2–15.0)	7.7 (3.1–16.6)
TL (ankle to AbH) (msec)	107	4.3 (3.3–6.0)	4.2 (3.2–6.0)	143	4.4 (3.4–6.2)	4.4 (3.4–6.4)
FWL (ankle st.) (msec)	70	44.6 (38.5–51.5)	44.5 (38.5–51.7)	140	50.8 (43.1–60.2)	51.0 (42.7–58.6)
MCV (ankle-popliteal fossa) (m/sec)	107	47.6 (41.8–54.8)	48.6 (42.2–54.1)	143	41.0 (32.0–48.8)	40.0 (33.0–49.0)
FCV (ankle st.) (m/sec)	70	54.9 (47.8–64.4)	55.0 (48.1–63.9)	139	47.0 (40.0–56.0)	47.0 (39.0–56.0)
Median nerve, sensory						
SNAP amplitude (wrist st.) (μV)	103	34.0 (14.1–58.5)	35.0 (13.7–57.0)	126	14.3 (4.2–38.9)	14.4 (3.9–42.1)
SCV (wrist-elbow) (m/sec)	103	65.2 (57.2–70.7)	65.0 (58.0–71.6)			
SCV (finger-wrist) (m/sec)	103	57.3 (48.2–65.2)	57.7 (47.1–68.0)	126	48.5 (33.0–60.0)	48.0 (33.0–60.0)
Sural nerve						
SNAP amplitude (μV)	101	15.9 (7.5–32.7)	17.4 (6.8–30.4)			
SCV (mid calf-ankle) (m/sec)	101	52.0 (42.0–60.6)	52.2 (43.5–61.8)			

st. = stimulation

jects and patients with DPN to help design future drug assessment protocols.

The San Antonio conference on diabetic neuropathy recommended the inclusion of F-wave in the battery of electrodiagnostic test [7]. Other studies have shown that F-wave serves as a sensitive indicator of DPN [8, 9]. We wished to establish the reproducibility of F-wave latency as an important measure for evaluating the serial change of nerve conduction in DPN patients.

Subjects and methods

Healthy subjects. We studied the left median and tibial nerves for motor conduction, and left median and sural nerves for sensory conduction. All measurements were repeated twice with a time interval of 1–2 weeks in 132 healthy subjects (63 men) aged between 34 and 66 years (mean 50 years). The study was conducted by the same examiner in each of 32 neurophysiological laboratories from September 1991 to April 1992. The number of subjects tested in each laboratory ranged from 2 to 12 (mean 4.1).

A conventional, standardised method was used to measure terminal latency (TL) and amplitude of compound action potential (CMAP) with distal stimulation and to calculate motor nerve conduction velocity (MCV). For the median nerve, CMAP was recorded from the abductor pollicis brevis muscle with the active lead (G1) placed on the belly of the muscle and the reference lead (G2) 4 cm distally. Stimulation was delivered at the wrist, 6 cm proximal from G1, and at the elbow just lateral to the insertion of the biceps tendon. For the tibial nerve, CMAP was recorded from the abductor hallucis with G1 placed on the belly and G2, 5 cm distally. Stimulation was delivered posterior to the medial malleolus, 9 cm from G1 and at the popliteal fossa. Minimal F-wave latency (FWL) was selected from at least eight tracings obtained by supramaximum stimuli delivered distally. Based on this latency, F-wave conduction velocity (FCV) was calculated using the previously described formula: $D \times 2/(FWL\text{-}TL\text{-}1)$; where D is the estimated distance from the stimulus site to the spinal cord [10].

Sensory nerve conduction studies included the measurements of the amplitude with distal stimulation and calculation of sensory conduction velocity (SCV). Sural nerve sensory nerve action potential (SNAP) was recorded antidromically with G1 placed posterior to the lateral malleous and G2, 5 cm distally, after stimulation of the nerve over the posterior aspect of the leg, 13 cm proximal from G1. Median nerve SNAP was recorded with ring electrodes placed around the proximal (G1) and the distal (G2) interphalangeal joints of the index finger. Stimulation was applied at the wrist, 15 cm from G1, and at the elbow joint lateral to the biceps tendon.

Stimulus intensity was adjusted to 20% above the strength which produced a maximum response. Signals were amplified with a bandpath 15 or 30 Hz to 3 kHz.

Patients with diabetic polyneuropathy (DPN). A total of 172 patients with DPN (99 men), aged between 20 and 69 years (mean, 56 years), participated in the study conducted at 65 neurophysiological laboratories from July 1994 to March 1995. The number of patients tested in each laboratory ranged from 1 to 9 (mean 2.6). All measurements were repeated twice with a time interval of 1 to 4 weeks. There were 10 insulin-dependent, 161 non-insulin-dependent and 1 pancreatic diabetes

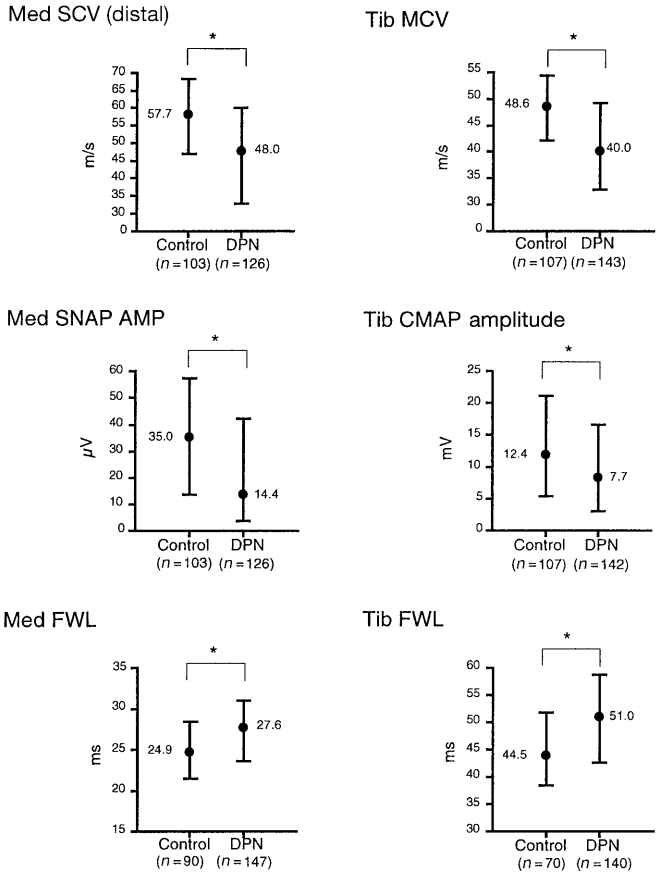


Fig. 1. The median value with 5th to 95th centile range of the measurements in healthy subjects and patients with DPN. Med = median nerve, Tib = tibial nerve. $*p < 0.0001$ (Wilcoxon's signed rank test)

patients. All had typical clinical symptoms and signs including numbness, dysesthesia or hypesthesia of the feet and a decreased or absent achilles tendon reflex. All had a clinically stable course during the study with a mean HbA_{1c} of $8.5 \pm 2.1\,\%$. Because the study was designed for future drug trials, patients with very advanced disease were excluded with admission of only those having a conduction velocity of the tibial nerve more than 30 m/s and the CMAP amplitude larger than 2 mV. To keep each session short, we omitted sural nerve measurements and median nerve studies of CMAP and calculation of MCV from the patient protocol based on our earlier experience in healthy subjects.

In both healthy subjects and patients with DPN, skin temperature was controlled to 31 °C or higher in the upper limb and 30 °C or higher in the lower limb. Each centre was instructed to keep the temperature as constant as possible for the first and second trials by warm water, electric blanket or heating lamps. As a result, we were able to maintain very small differences between the two sessions, with variabilities of less than 1.0 °C in most (> 80 %) subjects.

All subjects gave informed consent to the protocol prepared in accordance with the Declaration of Helsinki.

In preparation for the studies, hands-on workshops were held to familiarise all examiners in this project with the standardised method. Each participating laboratory forwarded all electrophysiological data for quality inspection of the waveform at the centre. Tracings with various technical problems were removed based on the predetermined exclusion criteria which included:

1. Large noise or stimulus artefact or unphysiologic waveform.
2. Submaximum intensity of distal or proximal stimulation.
3. Deviation of skin temperature outside the established range.
4. Excessive alteration of waveform between the first and second trial.
5. Evidence of peripheral neuropathy in the control subjects.
6. Evidence of non-diabetic neuropathy in the patient group.

Statistical analyses. We used two methods of analysis [1, 11, 12], the relative intertrial variation (RIV) and intraclass correlation coefficient (ICC), to assess the precision and the reliability of the measurements. All analyses were done using SAS software system (SAS Institute, Carey, N.C., USA). Two-tailed p values of 0.05 or less were considered to indicate a statistical significance.

RIV. The following value was first calculated for each patient:

$$100(V2–V1)/0.5(V1 + V2)$$

where V1 and V2 represent the values of the first and the second measurements of the pair. The relative intertrial variation (RIV) is defined as the range from the 5th per centile value to the 95th per centile value of values calculated by above method to exclude unexpected outliers. It directly represents a variation of measurements expressed as the percentages of the difference between V1 and V2 over the mean value of repeated measurements. The RIV from –10 % to 10 % represented measurements with higher precision.

ICC. Measures having a larger interindividual variability are expected to show a greater intraindividual variability as well. The model of ICC is designed to take this effect into consideration. The ICC is defined as the proportion of variance attributable to variability among subjects, from 0 (all variability is experimental error) to 1 (no experimental error).

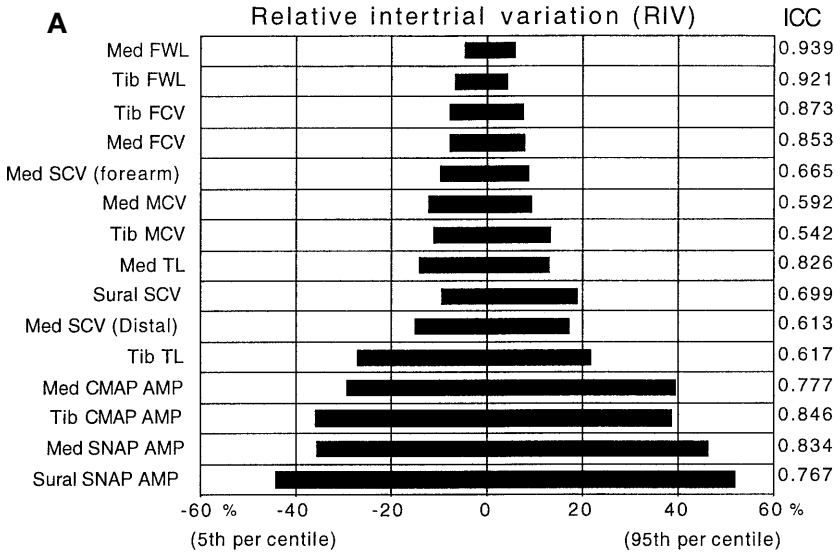
$$ICC = \sigma s^2/(\sigma s^2 + \sigma \varepsilon^2)$$

The components σs^2 and $\sigma \varepsilon^2$ have been estimated by analysis of variance. This calculation indicates that if there is large experimental error, ICC will be small. We defined measurements with ICC more than 0.9 as reliable.

Because none of the measurements showed a significant difference between non-insulin-dependent and insulin-dependent diabetes, we combined the two groups of patients for statistical analysis.

Results

Table 1 shows the median value with the 5th to 95th per centile of the measurements in healthy subjects and patients with DPN. There is a significant difference between the two groups in all measurements ($p < 0.0001$, Wilcoxon's signed rank test) except for the tibial nerve terminal latency ($p = 0.1043$) (Fig. 1). Here, the value of the second trial is used as the value representing each subject. The most sensitive of all



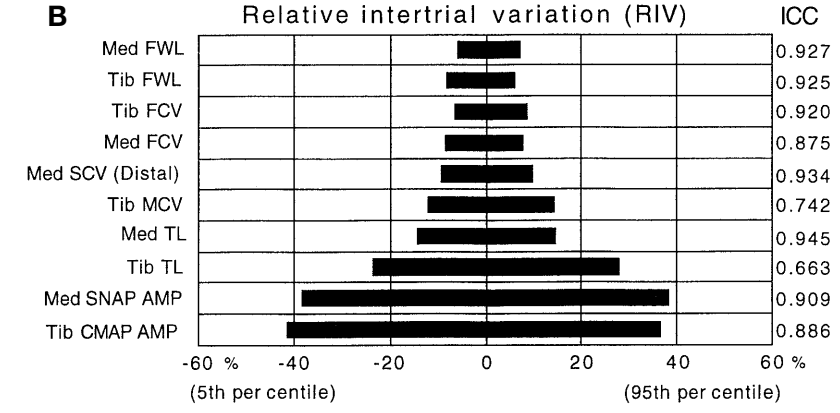


Fig. 2 A, B. RIV and ICC in healthy subjects (**A**) and patients with DPN (**B**). Measurements are sorted by RIV. Med = median nerve, Tib = tibial nerve, Sural = sural nerve, AMP = amplitude

were SCV, SNAP amplitude, FWL, FCV of the median nerve and MCV and FCV of the tibial nerve, showing large differences between healthy subjects and patients with DPN.

Figure 2 shows RIV and ICC in both groups and Figure 3 illustrates some examples of the individual data from the patients. The measures showing RIV of less than ± 10 % were the FWL and FCV of both median and tibial nerve; and wrist to elbow SCV of the median nerve in healthy subjects and FWL and FCV of both median and tibial nerves and wrist to finger SCV of the median in the patients. In general, amplitudes showed a greater variation than latencies or nerve conduction velocities. For example, median SNAP amplitude showed a large RIV; from –35.7 % to + 46.2 % in healthy subjects and from –38.2 % to + 38.3 % in patients with DPN.

The ICC was large (> 0.9) for FWL of both median and tibial nerves in healthy subjects, and for FWL of the median and tibial nerves, TL and SCV of the median nerve and FCV of tibial nerve in patients with DPN (Fig. 2). In contrast, ICC was small for MCVs in general, TLs for tibial nerve and SCV of sural nerve.

Median nerve SNAP amplitude had a large RIV (–38.2 to + 38.3 %) in patients with DPN, despite a fairly large ICC (0.909). This unexpected combination also characterises a few other amplitude measurements, i. e. median nerve CMAP in healthy subjects and tibial nerve CMAP in healthy subjects and patients with DPN (Figs. 2, 3). The large variance of the amplitudes can explain these seemingly contradictory findings: if σs is extremely larger than $\sigma\varepsilon$, ICC will become large as seen from the formula.

In summary, FWL of the median and tibial nerves showed a large ICC (> 0.9) combined with a small RIV (± < 10 %) in both healthy subjects and patients with DPN. The FCV of the tibial nerve and SCV of

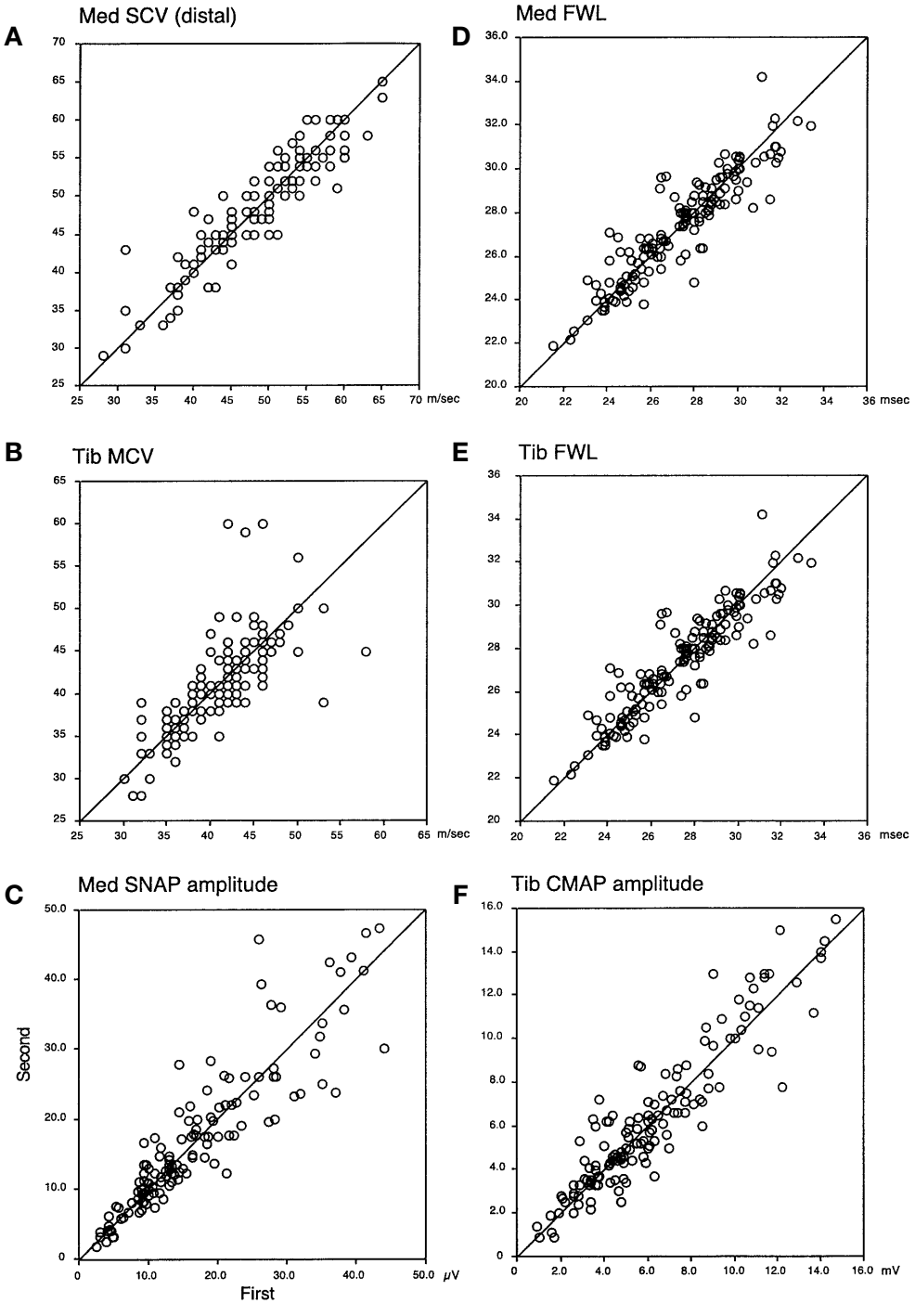


Fig. 3. The relation between the first and the second measurements in patients with DPN. Horizontal line indicates the value of the first measurement and vertical the second. Values of intraclass correlation coefficient (ICC) and relative intertrial variation (RIV) were as follows: **A** ICC = 0.934, RIV = –9.1 ~ 9.8 %, **B** ICC = 0.742, RIV = –12.0 ~ 14.2 %, **C** ICC = 0.909, RIV = –38.2 ~ 38.3 %, **D** ICC = 0.927, RIV = –5.8 ~ 7.2 %, **E** ICC = 0.925, RIV = –8.0 ~ 6.0 %, **F** ICC = 0.886, RIV = –41.4 ~ 36.5 %. (Med, median nerve; Tib, tibial nerve)

the median nerve also showed the same reliability characteristics, but only in patients with DPN (Fig. 3).

Discussion

The results of our study show that of all the measurements, F-wave latency yielded the highest ICC with the smallest RIV for both median and tibial nerves in both healthy subjects and patients with DPN. Several studies reported on the reliability of nerve conduction in healthy subjects [10–18] and patients with

DPN [1, 2, 4–6, 19]. All but two [2, 6] were conducted in a single laboratory and few studied F-waves [1, 2, 5]. A French multicentre study in patients with DPN [2] found less variability of median and peroneal nerve MCV. It also yielded an excellent coefficient of variation of the median and peroneal nerve FWL and poor reproducible amplitude for both motor and sensory nerves. Another study [1] found an ICC of less than 0.7 for median CMAP amplitude, FWL of the median nerve and TL of the tibial nerve. Their results are in agreement with ours except the small ICC of the median nerve FWL.

The ICC has been considered the best statistical assessment to compare different kinds of measurements with different units [1, 11]. As shown in the results of the median nerve SNAP amplitude in patients with DPN, a large ICC does not, however, necessarily imply a good reproducibility. From a clinical point of view, any measurement with a large RIV is inappropriate for a sequential study. Thus we considered it necessary to calculate RIV to exclude these measurements.

Principal factors contributing to an intertrial variability include inadequate control of skin temperature, insufficient stimulus intensity, errors in determining the latency or measuring the surface distance, and difficulty in placing recording electrodes exactly at the same place on two separate occasions [13–17]. Amplitudes vary most probably because of a shift in the recording site. Technical difficulties in stimulating the tibial nerve at the ankle, especially in obese subjects, could account for a large variance on the terminal latencies.

Of all the measurements, FWL showed the smallest RIV with large ICC both in healthy subjects and patients with DPN. The F-wave is a late response occurring after the direct motor potential (M response), and results from the backfiring of antidromically activated anterior horn cells [10]. The FWL registers a conduction time over a longer segment of the nerve. Thus compared with TL or MCV over a shorter segment, the same measurement error in latency contributes less in percentage. The SCV showed large ICC only in patients with DPN. This is partly because of the larger variance of SCV in subjects with DPN compared with healthy ones.

For serial clinical evaluations of polyneuropathy, both the reproducibility and sensitivity of the measurements are essential. Although our studies did not test the sensitivity systemically, the median value of FWL and FCV in patients with DPN was statistically significantly prolonged compared with that in healthy subjects as well as NCV. Several studies have also shown FWL or FCV to be sensitive indicators of DPN [8, 9, 20]. The FWL is increased and FCV is decreased over both the proximal and distal segment, although the abnormality is more prominent distally [8]. In one study comparing the diagnostic yields of various aspects of nerve conduction studies, FWL was found most sensitive in patients with DPN [9]. Thus the highly reproducible FWLs could be one of the best measures in multicentre drug trials for diabetic polyneuropathies.

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