

Amplitude of sensory nerve action potential in early stage diabetic peripheral neuropathy: an analysis of 500 cases

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Abstract

Early diagnosis of diabetic peripheral neuropathy is important for the successful treatment of diabetes mellitus. In the present study, we recruited 500 diabetic patients from the Fourth Affiliated Hospital of Kunming Medical University in China from June 2008 to September 2013; 221 cases showed symptoms of peripheral neuropathy (symptomatic group) and 279 cases had no symptoms of peripheral impairment (asymptomatic group). One hundred healthy control subjects were also recruited. Nerve conduction studies revealed that distal motor latency was longer, sensory nerve conduction velocity was slower, and sensory nerve action potential and amplitude of compound muscle action potential were significantly lower in the median, ulnar, posterior tibial and common peroneal nerve in the diabetic groups compared with control subjects. Moreover, the alterations were more obvious in patients with symptoms of peripheral neuropathy. Of the 500 diabetic patients, neural conduction abnormalities were detected in 358 cases (71.6%), among which impairment of the common peroneal nerve was most prominent. Sensory nerve abnormality was more obvious than motor nerve abnormality in the diabetic groups. The amplitude of sensory nerve action potential was the most sensitive measure of peripheral neuropathy. Our results reveal that varying degrees of nerve conduction changes are present in the early, asymptomatic stage of diabetic peripheral neuropathy.

Key Words: nerve regeneration; peripheral nerve injury; diabetic peripheral neuropathy; neural conduction; electrophysiology; sensory nerve; motor nerve; early diagnosis; neural regeneration

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Introduction

Diabetic peripheral neuropathy is the most common chronic complication of diabetes mellitus, with an incidence rate of about 50 % (Shi et al., 2013; Galuppo et al., 2014; O'Brien and Kareem, 2014; Won et al., 2014; Zhong et al., 2014). Once symptoms appear, there are few effective therapeutic strategies (Won et al., 2014). Therefore, early discovery and diagnosis are extremely important. Nerve conduction studies are the most common method for diagnosis of peripheral neuropathy (An et al., 2007; Kincaid et al., 2007; Koçer et al., 2007; Severinsen and Andersen, 2007; Kiziltan and Benbir, 2008; Løseth et al., 2008, 2010; Uluc et al., 2008; Asad et al., 2009; Hemmi et al., 2009; Watanabe et al., 2009; Charles et al., 2010; Dyck et al., 2010; Lee et al., 2010; Suh et al., 2010; Watanabe et al., 2010; Altun et al., 2011; Dyck et al., 2011; Koytak et al., 2011; Shin et al., 2011; Heise et al., 2012; Mondal et al., 2012; Morimoto et al., 2012; Spadella et al., 2012; Arimura et al., 2013; Joa and Kim, 2013; Koo et al., 2013; Richardson et al., 2013; Chiles et al., 2014; McLellan et al., 2014). Heise et al. (2012) found that the combined in-

dex, comprising five parameters of nerve conduction, had greater sensitivity and equivalent specificity compared with individual parameters in the detection of diabetic polyneuropathy. In another study, Erdoğan et al. (2011) found that the strength-duration time constant may be useful in the early stages of neuropathy, since most patients with diabetic neuropathy had predominant changes in this parameter in their lower extremities. In our previous electrophysiology studies, we used several indices that are routinely measured in diabetic and suspected diabetic patients, with the aim of facilitating early diagnosis of diabetic peripheral neuropathy, reducing treatment costs and improving therapeutic success. In the present study, we sought to establish a sensitive index for nerve conduction studies in the early diagnosis of peripheral neuropathy in 500 patients with diabetes mellitus.

Subjects and Methods

Subjects

500 diabetic patients who visited the doctor's office in the

Table 1 Demographic information of diabetic patients and control subjects

Item	Diabetic patients		Control subjects
	Asymptomatic group	Symptomatic group	
<i>n</i>	279	221	100
Gender (<i>n</i> , male/female)	151/128	115/106	48/52
Age (year)	62.3±8.8(34–87)	64.8±9.0(37–89)	61.1±10.8(32–78)
Course of disease (year)	7.7(0.8–18)	8.1(0.1–21)	–

Fourth Affiliated Hospital of Kunming Medical University in China from June 2008 to November 2013 were recruited by advertisement. All patients' conditions were consistent with the diagnostic criteria for diabetes, approved by the World Health Organization (Wendland et al., 2012). One hundred healthy control subjects who went to the doctor's office for other medical reasons were also recruited. Exclusion criteria: (1) peripheral neuropathy due to severe liver and kidney diseases, nutrition deficiency, connective tissue diseases and other metabolic or hereditary diseases; (2) radiculopathy due to cervical spondylosis and lumbar intervertebral disc protrusion; (3) history of long-term alcohol consumption or prolonged contact with poisonous substances (such as heavy metals) that could result in peripheral impairment; (4) history of drugs (such as isoniazid and furaxone) that may affect neural function. According to the symptoms of peripheral nerve impairment (such as numbness, pain, weakness, or burning cooling sensations in the limbs), the diabetic patients were divided into two groups, symptomatic and asymptomatic. One hundred healthy control subjects were also recruited by advertisement. There were no significant differences in disease course between the two groups of patients with diabetes, and no significant differences in gender, age, body height or weight among all three experimental groups ($P > 0.05$; **Table 1**).

The procedures were in accordance with institutional and regional ethical standards of responsible experimentation and with the *Helsinki Declaration* of 1975. The Chinese Ethics Committee approved the age range of adult research participants and obtained consent for children aged over 7 years participating in the trial. Subject approval was obtained for the electrophysiological test procedures, which were in accordance with the guidelines of the Chinese Ethics Committee.

Analysis of neural conduction

Each subject lay on a bed in a quiet room (22–25°C) with limbs relaxed. Skin temperature was maintained above 32°C. Electromyography/evoked potential apparatus (Dantec Dynamics, Skovlunde, Denmark) was employed in nerve conduction studies. Motor and sensory nerve conduction of unilateral or bilateral median nerve, ulnar nerve, posterior tibial nerve and common peroneal nerve were measured separately. In the motor nerve conduction test, the sellar stimulus electrode was placed in front of the stylomastoid foramen, with the negative pole of the electrode placed at the distal end of the nerve. The surface electrode was placed at the proximal end of the nerve, on the muscle belly of the

frontalis, nasalis or orbicularis oris muscles. The groundwire was placed between the stimulus and recording electrodes. For sensory nerve conduction tests, a ring electrode was placed around the end of the fingers or toes, that is, the distal end of the sensory nerve, and used to stimulate the median, ulnar and posterior tibial nerves. A surface electrode was employed to stimulate the common peroneal nerve. The recording electrode was placed at the proximal end of the spinal cord using the antegrade method, described previously (Cui, 2006). Detection parameters were: amplitude of compound motor action potential, distal motor latency, amplitude of sensory nerve action potential, and sensory nerve conduction velocity. Control values corresponded to the standards of electromyography for age and gender in Peking Union Medical College Hospital in China (Zhang et al., 2013).

Statistical analysis

Data were analyzed using SPSS 11.5 software (SPSS, Chicago, IL, USA) and presented as mean ± SD. Paired *t*-tests were used to compare measurement data. Numeration data are expressed as numbers of nerve fibers (%). A chi-square test was used to compare rates between two samples. $P < 0.05$ was considered statistically significant (We used analysis of variance to compare the data of two experimental groups and control, and got similar outcome to those of paired *t*-tests, so we adopted the results of *t*-test as the final statistical outcome).

Results

Motor and sensory nerve conduction in patients with diabetic peripheral neuropathy

Distal latency of motor nerve conduction in the median, ulnar, posterior tibial and common peroneal nerve was longer in the asymptomatic diabetic group than in healthy controls, and the amplitude of compound motor action potential was significantly lower compared with that of the control group ($P < 0.05$; **Figure 1A**). Distal motor latency in the median and common peroneal nerves in the symptomatic group was markedly longer than in the asymptomatic group, and compound motor action potential amplitude in the median and common peroneal nerve was significantly lower in the symptomatic group than in asymptomatic patients ($P < 0.05$; **Figure 1B**).

Similarly to the sensory nerve conduction comparison in the median, ulnar, posterior tibial and common peroneal nerve, sensory nerve action potential amplitude and

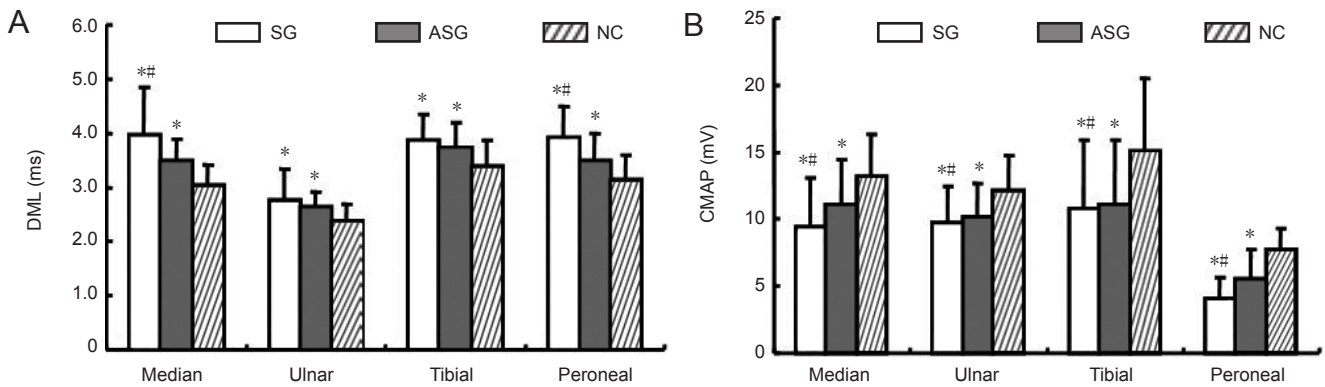


Figure 1 Motor nerve conduction in diabetic patients with/without peripheral neuropathy and in control subjects. (A) Distal motor latency (DML); (B) compound muscle action potential (CMAP). Data are presented as mean \pm SD. * $P < 0.05$, vs. NC; # $P < 0.05$, vs. ASG (paired t -test). SG: Symptomatic group ($n = 221$); ASG: asymptomatic group ($n = 279$); NC: normal control group ($n = 100$).

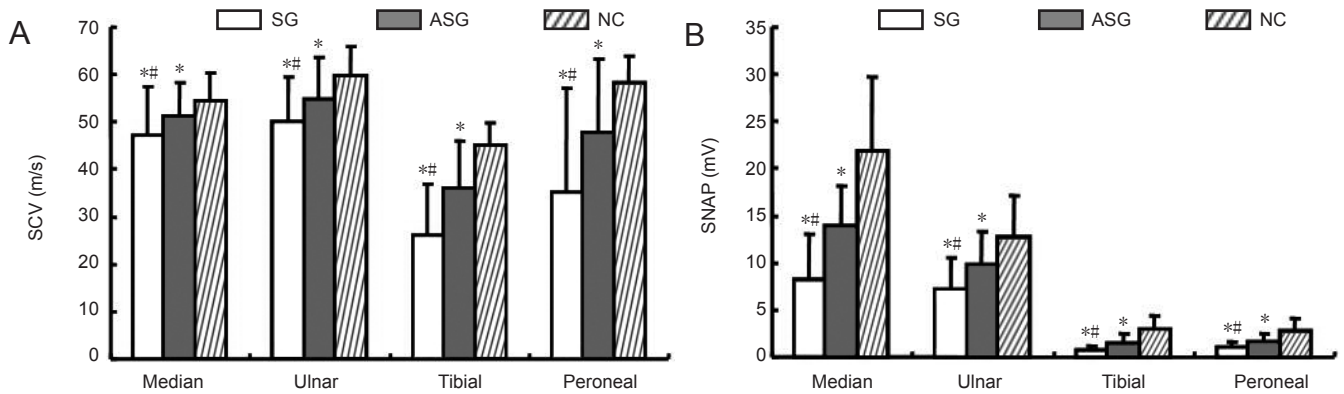


Figure 2 Sensory nerve conduction in diabetic patients with/without peripheral neuropathy and in control subjects. (A) Sensory nerve conduction velocity (SCV); (B) sensory nerve action potential (SNAP). Data are presented as mean \pm SD. * $P < 0.05$, vs. NC; # $P < 0.05$, vs. ASG (paired t -test). SG: Symptomatic group ($n = 221$); ASG: asymptomatic group ($n = 279$); NC: normal control group ($n = 100$).

Table 2 Abnormal distribution (%) of motor and sensory nerve conduction in diabetic patients with/without peripheral neuropathy and in control subjects

Nerve	Number of nerve fibers	Total abnormality	Motor nerve conduction			Sensory nerve conduction			χ^2	P
			No wave	DML	CMAP	No wave	SCV	SNAP		
Median	972	52.9	0.3	16.4	13.0	10.6	32.9	42.3	281.006	< 0.05
Ulnar	953	34.5	0	1.8	2.1	0.9	2.9	33.6	334.908	< 0.05
Tibial	912	53.3	0.5	1.1	1.3	28.8	17.8	24.5	603.809	< 0.05
Peroneal	908	60.0	1.8	11.6	21.8	23.7	22.0	36.3	248.002	< 0.05

If amplitude and conductive velocity abnormalities occurred simultaneously in one nerve, one nerve conductive abnormality was counted. A chi-square test was used for comparison between two samples. DML: Distal motor latency; CMAP: compound motor action potential; SCV: sensory nerve conduction velocity; SNAP: sensory nerve action potential.

sensory nerve conduction velocity in both diabetic groups was significantly lower than in healthy controls ($P < 0.05$). Importantly, sensory nerve action potential amplitude and sensory nerve conduction velocity of the median, ulnar, posterior tibial and common peroneal nerves in the symptomatic group was significantly lower than in the asymptomatic group ($P < 0.05$; **Figure 2**).

Outcome analysis of nerve conduction studies

Of 500 diabetic patients, 358 (71.6%) exhibited nerve con-

duction abnormalities. The highest rate of abnormality was found in the common peroneal nerve, followed by the posterior tibial nerve and median nerve, with the ulnar nerve showing the lowest rate of abnormality ($P < 0.05$). In the motor nerve conduction tests, the common peroneal nerve showed the highest rate of absent waveforms, whereas in sensory nerve conduction tests, the posterior tibial nerve was found to have the highest rate of absent waveforms. The most sensitive index for nerve conduction studies in diabetic patients was sensory nerve action potential, followed by

sensory nerve conduction velocity; compound motor action potential and distal motor latency had relatively low sensitivity. Among the nerve conduction indices, the highest rate of abnormality was found in median nerve sensory nerve action potential (Table 2).

Discussion

Diabetic peripheral neuropathy commonly develops insidiously, with various clinical manifestations. In the early stages, diagnosis is difficult as there are no symptoms. Fortunately, increasing use of electrophysiological techniques that allow the identification of sub-clinical pathological changes has made early diagnosis of diabetic peripheral neuropathy possible (Liu et al., 2005; Al-Geffari, 2012; Balbinot et al., 2012; Barriga et al., 2012; Gulichsen et al., 2012; Kuntzer et al., 2012; Calvet et al., 2013; Fang et al., 2013; Mete et al., 2013; Papanas et al., 2013; Sellers et al., 2013; Sun et al., 2013; Gordon Smith et al., 2014). Electrophysiology has the advantages of being objective and sensitive, allowing the scope and extent of affected peripheral nerves to be precisely ascertained and providing a conclusive diagnosis of diabetic peripheral neuropathy. Indeed, nerve conduction studies have become an indispensable tool in the discovery of peripheral nerve abnormalities. In patients with diabetic peripheral neuropathy, the main abnormality in nerve conduction studies manifests as reduced amplitude, slowed conductive velocity or prolonged latent phase, and in severe cases the waveform is eliminated entirely.

In the present study, we found that the total abnormal nerve conduction rate in both diabetic groups was 71.6%, which was in accordance with a previous report (Banthia et al., 2013). Distal motor latencies in the median, ulnar, posterior tibial and common peroneal nerves in the asymptomatic group were significantly prolonged compared with those in the control group. Sensory nerve conduction velocity and amplitudes of sensory nerve action potential and compound motor action potential were all markedly lower in the asymptomatic group than in controls, suggesting that impairment of sensory and motor axons and the myelin sheath at the distal end already exists in the early stages of diabetic peripheral neuropathy, before symptoms emerge. In the symptomatic group, sensory nerve conduction velocity was notably slower, distal motor latency in the median and common peroneal nerves was significantly prolonged and the amplitude of compound motor action potential was lower than in the asymptomatic group. These observations indicate that after symptomatic peripheral nerve impairment emerges in diabetic patients, lesions in the sensory fibers of the median, ulnar, posterior tibial and common peroneal nerve, and in the neuraxis and myelin sheath of motor fibers of the common peroneal nerve, are markedly aggravated compared with the asymptomatic stage. Importantly, we show for the first time that in both groups of diabetic patients, sensory nerves were affected to a greater extent than motor nerves, indicating that sensory nerves are more vulnerable to damage than motor nerves in diabetic peripheral neuropathy. In the diabetic groups, posterior tibial and common peroneal

nerve conduction in the lower extremities had a markedly higher rate of absent waveforms than the median and ulnar nerves of the upper extremities, implying that the extent of nerve fiber lesions in the lower extremities is more severe than that in the upper extremities in diabetic patients. Importantly, we show for the first time that although diabetic peripheral neuropathy leads to diffuse conductive abnormality across whole peripheral nerves, the nearer the damage is to the distal end, the more severe the extent of impairment.

The total rate of abnormality detected in the median, ulnar, posterior tibial and common peroneal nerves in diabetic patients was 60%. The common peroneal nerve was the most prominently affected. Moreover, among all patients with diabetes, the common peroneal nerve showed the highest rate of absent waveforms, indicating that among the lesioned peripheral motor nerves in diabetic patients, the common peroneal nerve was most severely damaged. The posterior tibial nerve was most severely impaired from the sensory nerve tests. Comparing all indices of nerve conduction studies, we found that sensory nerve action potential was the most sensitive index. In the present study, the median nerve showed the highest rate of sensory nerve action potential abnormality, suggesting that this nerve is the first to be affected in diabetes. To our knowledge, we are the first to show a conclusive and simple relationship between peripheral nerve lesions and electrophysiological indices in different nerves commonly affected in diabetic peripheral neuropathy. In practical terms, this will enable earlier diagnosis of the condition.

Liu et al. (2005) studied 700 patients with diabetic peripheral neuropathy using nerve conduction studies and found that the longer the duration of the disease, the greater the possibility that abnormal electrophysiology will be observed. The electrophysiological abnormalities observed in the present study may be attributed to nutritional and metabolic disorders resulting from the diabetes itself, leading to impairment of axoplasmic transport in peripheral nerves, preventing distal axons from acquiring sufficient nutrition and ultimately leading to their degeneration. In a study by Bi et al. (2008), it was revealed that sensory nerve action potential amplitude is more sensitive than nerve conduction velocity in the diagnosis of mild or early diabetic peripheral neuropathy. Our study confirmed this notion. Importantly, we found that the abnormal rate of sensory nerve conduction velocity in diabetic patients was much higher than that of motor nerve conduction velocity, corresponding with previous studies (Tan and Tan, 2003; Kles and Bril, 2006; Vinik et al., 2006; Bi et al., 2008; Charles et al., 2013). These results indicate that nerve conduction studies should be used as an important index for the early diagnosis of diabetic peripheral neuropathy.

Taken together, our data demonstrate that various degrees of peripheral neuropathy occur in both sensory and motor nerves in the early stages of diabetes, before symptoms occur. The extent of impairment in the lower extremities is more severe than that in the upper extremities. Importantly, the extent of the lesion in sensory nerves is more severe than that in motor nerves. Symptoms and sensory nerve impair-

ment will worsen with time; therefore, nerve conduction, especially sensory nerve action potential detection, should be routinely examined in diabetic patients so that diabetic peripheral neuropathy can be discovered and treated as early as possible.

Author contributions: Zhang YQ was responsible for electrophysiological test. Li JT was responsible for manuscript writing, revision and trial design. Wang TJ was responsible for experimental collection and statistical analysis. Wang JL was responsible for trial design, examination and verification of the experimental data, determination of the final draft of this manuscript. All authors approved the final version of the paper.

Conflicts of interest: None declared.

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