

Current perception threshold in diabetic sensory polyneuropathy with normal routine nerve conduction study

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Received: March 6, 2017

Revised: June 19, 2017

Accepted: June 22, 2017

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Background: Routine nerve conduction study (NCS) can only be used to evaluate the function of large fibers, and the results of NCS are often normal in patients with distal sensory polyneuropathy. The measurement of the current perception threshold (CPT) has been reported to represent a variety of peripheral nerve fiber functions. This study was performed to investigate the value of measuring CPT in patients with diabetic sensory polyneuropathy who have no abnormalities in routine NCS.

Methods: Twenty-seven diabetic patients with sensory polyneuropathy and normal routine NCS and 18 age-matched control subjects participated in this study. The CPT was measured on the unilateral index finger and great toe of each subject at frequencies of 5 Hz, 250 Hz, and 2,000 Hz.

Results: CPT values were significantly higher in the patient group than in the control group, especially with stimuli at the lowest frequency of 5 Hz ($p < 0.05$). There were significant correlations between the CPT values obtained at three different frequencies in the patient group, whereas the correlation was only significant in the pair of 250 Hz/5 Hz (both in the hands and feet), and in the pair of 2,000 Hz/250 Hz (in the feet) for the control group.

Conclusions: Our data suggest that the CPT test, especially at a stimuli frequency of 5 Hz, may be a useful screening tool for diabetic polyneuropathy in patients who show no abnormalities in routine NCS.

Key words: Current perception threshold; Diabetic neuropathies; Nerve conduction study

INTRODUCTION

Sensory polyneuropathies are frequently encountered in clinical practice,¹ but their confirmation is not always straightforward, especially during the early stages of the disease, due to the inability of routine nerve conduction study (NCS) to detect small nerve fiber dysfunction.² NCS in the sural nerve has been reported to fail to reveal any conduction abnormalities in 38 to 77% of patients with clinically suspected sensory polyneuropathies.^{3,4} Thus, special techniques that can be used to facilitate the diagnosis, including interdigital and plantar NCS,⁵⁻⁷ intraepidermal nerve fiber assessment,⁸⁻⁹ corneal confocal microscopy,¹⁰ and recently *in vivo* reflectance confocal microscopy of Meissner corpuscles,¹¹ are actively being pursued. However, these studies are limited by several factors, including the degree of invasiveness and pain or the need for special equipment and expertise.

Quantitative sensory testing (QST) to determine the thresholds for light touch-pressure, vibration, and thermal stimuli would be another option for objectively demonstrating sensory deficits.¹² However, although it has been claimed to be reliable, QST requires the subject's full cooperation, and the results are dependent on the methodology used. The current perception threshold (CPT) test is a type of QST that is known to be quicker and much easier to use than other conventional assessment techniques.¹³⁻¹⁷ A transcutaneous electrical stimulator typically delivers sinusoidal electrical stimuli at frequencies of 5 Hz, 250 Hz, and 2,000 Hz. Several investigators have reported that the test could evaluate the function of a wide range of peripheral nerve fibers depending on the frequencies of the delivered stimuli, i.e., lower frequency stimuli are used to evaluate small fiber function, whereas higher frequency stimuli are used to evaluate large fiber function.¹³⁻¹⁹ The test has also been suggested as a good screening tool for discriminating between neuropathic and non-neuropathic patients with diabetes.^{13,14,18-20} However, no study has investigated the diagnostic value of CPT in patients with diabetic sensory polyneuropathy, specifically with respect to patients with normal routine NCS results. This study was performed to investigate whether the CPT test can differentiate this mild neuropathic group of patients from control subjects. In addition, we also analyzed whether the CPT values obtained with stimuli of different frequencies can truly represent the function of different peripheral nerve fiber populations.

MATERIALS AND METHODS

Subjects

Twenty-seven patients with diabetic sensory polyneuropathy and 18 age-matched controls were included in this investigation. The diagnostic criteria for diabetic sensory polyneuropathy included: (1) no cause of polyneuropathy other than diabetes mellitus, (2) symmetric complaints of paresthesia or numbness in the feet and/or distal lower legs, (3) symmetric sensory impairment in the feet and/or distal lower legs, or symmetrically decreased stretch reflexes in the ankle, and (4) normal muscle power. Routine NCS was performed in all eligible patients, and only patients who showed normal test results were included. The control group consisted of non-diabetic subjects who did not have any signs or symptoms of peripheral neuropathy or a history of any condition that could cause peripheral neuropathy. This study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB No.: B-1703-385-102).

Methods

Eligibility (i.e., diabetic sensory polyneuropathy) was initially assessed by one of the authors based on a detailed history and careful neurological examination. Eligible patients were then assessed by routine NCS, which included the motor, sensory, and mixed nerve conduction studies in the unilateral ulnar and median nerves, the sensory nerve conduction in the bilateral sural nerves, the motor nerve conduction in the bilateral peroneal and posterior tibial nerves, and the F-waves in the ulnar, median, peroneal and posterior tibial nerves. NCS was performed using standard techniques of surface stimulation and recording (Nicolet Viking IV). Skin temperatures were maintained above 31.0°C. Distal motor latency, minimal F-wave latency, and motor nerve conduction velocity were measured. The distal stimulation distance was 5 cm for the median and ulnar nerves, 8 cm for the peroneal nerve, and 10 cm for the posterior tibial nerve. Sensory nerve conduction velocity was orthodromically measured in the median (from the index finger to the wrist) and ulnar (from the fifth finger to the wrist) nerves, and antidromically obtained in the sural (from the midcalf to the lateral malleolus) nerve. Sensory nerve conduction velocity was determined from the peak latency. F-wave latencies

were corrected for the patient's age and height. Laboratory investigations, including vitamin B12, thyroid function test (T4/T3/TSH), venereal disease research laboratory (VDRL), anti-human immunodeficiency virus (HIV) antibody, serology for hepatitis B and C, and protein electrophoresis (serum and urine), were performed to exclude other causes of sensory polyneuropathy. Ancillary tests, such as needle electromyography (EMG), somatosensory evoked potentials and magnetic resonance imaging, were performed appropriately, if needed, to exclude other causes mimicking distal sensory polyneuropathy, such as bilateral lumbosacral radiculopathy and myelopathy.

Neurometer (Neurotron Inc., Baltimore, MD, USA) was used to measure the CPTs. Previous studies have reported the usefulness of this device for the evaluation of peripheral nerves in various diseases including diabetes mellitus.^{19,21} It delivers sinusoidal alternating current stimuli at three different frequencies: 5 Hz, 250 Hz, and 2,000 Hz. Current intensity ranges from 0.01 to 9.99 mA.^{13,15,16,22} The current stimuli were applied to unilateral dorsal surfaces of the distal phalanges of the index finger and great toe via two small gold-plated electrodes with a diameter of 1 cm. Patients were seated in a quiet room and asked to report the presence or absence of electrical stimulation. At each frequency, the current was slowly increased until the subject first reported the perception of sensation. The current was then decreased and reincreased until a consistent threshold was measured.^{13,17} The operator who measured the CPT was blinded to the subjects' symptoms and signs as well as their diagnoses.

CPT values were expressed as mean \pm SD, and the Mann-Whitney U test was performed to compare the CPT values obtained from patients with those from control subjects. Spearman's rank correlation coefficient was used to evaluate the degree of correlation between the CPT values obtained with stimuli of different frequencies. Statistical significance was set at $p < 0.05$.

RESULTS

Clinical features

The patient group consisted of 12 men and 15 women, and their mean age was 61.6 years (range, 40 to 72 years). All of the patients suffered from type 2 diabetes mellitus. The av-

erage duration of disease was 6.6 years (range, 1 to 15 years), and the average HbA1c was 7.1% (range, 5.1 to 11.5%). Eighteen control subjects (6 men and 12 women) also participated in this study, and their mean age was 59.1 years (range, 52 to 68 years). The clinical features of the patients are summarized in Table 1. The most common sensory symptoms were a symmetric tingling sensation (93%) and numbness (85%) in the feet. A small proportion of the patients (15-19%) complained of a burning sensation or stabbing pain in the same region. Six patients (22%) complained of sensory symptoms in both the hands and feet.

CPT values at each frequency

Full evaluation of the test typically took 10 to 15 minutes. The CPT values obtained from the patient and control groups at each frequency are shown in Figure 1. At 5 Hz, the CPT values from the patient group were significantly higher than those from the control group in both the hands (1.2 ± 0.6 mA vs. 0.9 ± 0.3 mA, $p = 0.03$) and the feet (1.6 ± 0.7 mA vs. 1.0 ± 0.5 mA, $p = 0.002$). However, at higher frequencies, the CPT values in the patient group were significantly higher than those in the control group only for the feet at 250 Hz (2.2 ± 0.6 mA vs. 1.6 ± 0.5 mA, $p = 0.008$) and for the hands at 2,000 Hz (3.8 ± 1.0 mA vs. 3.3 ± 0.4 mA, $p = 0.048$).

Internal correlations between CPT values

The correlations between CPT values measured at three different frequencies were analyzed in each patient and the control group (Table 2). There were significant correlations

Table 1. Clinical symptoms and signs in the patient group

	Number of patients (%)
Symptoms	
Tingling sensation	25 (93)
Numbness	23 (85)
Burning pains	5 (19)
Stabbing pains	4 (15)
Signs	
Decreased pinprick or temperature sensation	22 (81)
Mildly decreased vibration or position sensation	4 (15)
Decreased or absent ankle jerks	14 (52)

Values are presented as n (%).

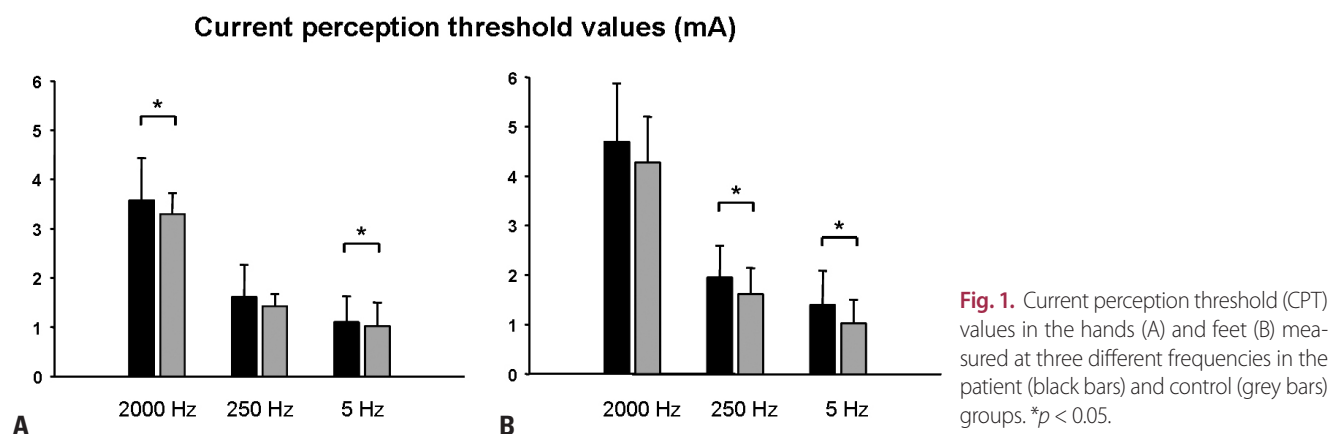


Table 2. Internal correlations of CPT values at different frequencies

	250 Hz/5 Hz	2,000 Hz/250 Hz	2,000 Hz/5 Hz
Hands			
Patient group	$r = 0.72$ ($p < 0.001^a$)	$r = 0.66$ ($p < 0.001^a$)	$r = 0.47$ ($p = 0.014^a$)
Control group	$r = 0.51$ ($p = 0.031^a$)	$r = 0.31$ ($p = 0.208$)	$r = 0.34$ ($p = 0.167$)
Feet			
Patient group	$r = 0.66$ ($p < 0.001^a$)	$r = 0.80$ ($p < 0.001^a$)	$r = 0.56$ ($p = 0.002^a$)
Control group	$r = 0.84$ ($p < 0.001^a$)	$r = 0.62$ ($p = 0.007^a$)	$r = 0.34$ ($p = 0.165$)

CPT, current perception threshold.

^aSignificance level $p < 0.05$.

between the CPT values measured at all three frequencies in the patient group, but there was only a significant correlation in the pair of 250 Hz/5 Hz (both in the hands and feet) and in the pair of 2,000 Hz/250 Hz (in the feet) in the control group. The correlation coefficients tended to be higher for the pairs of 2,000 Hz/250 Hz and 250 Hz/5 Hz than those for the pair of 2,000 Hz/5 Hz. Neither the recording site (hands or feet) nor the subject group (patient or control) affected this tendency.

DISCUSSION

In the present study, the CPT values were significantly higher in the patient group than in the control group, especially with stimuli at the lowest frequency of 5 Hz. The CPT values previously obtained from stimuli of 5 Hz and 250 Hz were suggested to represent the function of small sensory nerve (A-delta and C) fibers.¹³⁻¹⁹ Thus, the main pathology in our

patients was likely to be present in the small nerve fibers. In fact, the only clinical signs observed in the vast majority of patients were decreased sensibility to pinprick and thermal stimuli with preservation of other sensory modalities, such as vibration and position sensation. Therefore, we believe that the results of the CPT test in this study correspond well with the clinical features of the patients, and that the CPT values obtained from stimuli of 5 Hz and 250 Hz may aid in the detection of small nerve fiber dysfunction in the early stages of diabetic polyneuropathy. This contention was also supported by the fact that no abnormality suggestive of polyneuropathy was found in routine NCS of our patients.

It is well known that the CPT depends on various factors, such as the frequency and location of stimuli and age, in healthy individuals.^{13,22} As demonstrated in this investigation, the CPT value becomes greater as the frequency of stimuli increases, and it is higher in the feet than in the hands. However, as for the issue of whether the alternating current of different frequencies can truly stimulate different types of pe-

ipheral nerve fibers (i.e., fiber selectivity), there is no consensus among investigators, as only conflicting results have been reported thus far. Masson et al. compared CPT values with the results of conventional tests of peripheral nerve function, which showed that CPT at high frequency correlated best with tests of large fiber function, while CPT at low frequency correlated with tests of small fiber function.¹⁵ At 250 Hz and 2,000 Hz, the CPT was found to correlate best with the vibration perception threshold,^{17,19} while the CPT at 5 Hz stimulation was reported to have a significant negative correlation with the amplitude of the sympathetic skin response.¹⁸ However, in contrast, Vinik et al. reported that CPT values correlated well with the results of cutaneous sensory perception tests of both small and large nerve fiber functions in diabetic neuropathy patients and healthy controls, regardless of the stimuli frequency.²³ Veves and his coworkers also failed to show a correlation between the CPT and total myelinated nerve fiber density in the sural nerve.²⁴ In the present study, in order to address the issue of fiber selectivity, we analyzed the internal correlation between CPT at three different frequencies. We found that the internal correlation was weakest between CPT at the lowest (5 Hz) and highest (2,000 Hz) frequencies, which is in agreement with the findings of Pitei et al.¹⁷ Although it should be an indirect evidence at best, this result could support the notion that CPT at different frequencies may possibly stimulate different types of nerve fibers. Differences in the patients' characteristics regarding the selectivity of nerve fiber involvement might account for the inconsistency, and further large-scale systemic investigations are needed to verify the nerve fiber selectivity of the CPT test.

Another intriguing finding in the present study was that the CPT values obtained from 2,000 Hz stimuli were significantly higher in the patients than in the control subjects only for the hands and not for the feet. This seems to be contradictory to the length-dependent pattern of diabetic polyneuropathy, i.e., the feet are typically involved before the hands.²⁵ We speculated that subclinical compression or entrapment neuropathy involving the hands, such as carpal tunnel syndrome (CTS) and radial neuropathy, might have complicated our data. Mild CTS is often normal in routine NCS, and its confirmation requires additional median-ulnar or median-radial comparison tests. In addition, superficial radial sensory neuropathy, if any, might not have been detected since the nerve was not tested in our routine NCS. Kang et al. recently reported that CPT

at 2,000 Hz showed a significant correlation with CTS severity assessed by the Boston CTS questionnaire, which could foster a suspicion of CTS in our patients.²⁶ Interestingly, the authors could not find such a correlation for those at lower frequencies (250 Hz and 5 Hz), which might also account for the absence of a difference between CPT measures at 250 Hz in the hands in the present study.

Several limitations of this study should be acknowledged. First, the number of patients was too small to provide reliable data, especially on the diagnostic accuracy of the index test (i.e., CPT test), including its sensitivity and specificity. Second, the reference standard for the diagnosis of the disease, i.e., diabetic sensory polyneuropathy in this investigation, was based purely on clinical symptoms and signs. This could make the level of certainty in diagnosis somewhat questionable. However, this might be inherently related to the aim of the study, which was to assess the potential of the CPT test in patients with normal NCS results. However, future studies with the same goal as ours should use diagnostic tests, such as intraepidermal nerve fiber density, as the gold standard for diagnosing NCS-normal sensory polyneuropathy. Third, the control group was only age-matched. Therefore, although bias from a sex difference would not be large, it could not be ruled out. Finally, although the test is very quick and much easier to perform, it is also highly dependent on the full cooperation of the patient, as is the case with conventional QST, which may be difficult to obtain in elderly patients.¹² A relatively large test-to-test variability may be another concern, and it should be addressed in the future in a more systemic manner.²²

In conclusion, we found that the CPT was significantly higher in patients with diabetic polyneuropathy in whom routine NCS results were normal, especially when the stimuli was given at the lowest frequency of 5 Hz. Fiber selectivity depending on the frequency of current stimuli remains open to question, but our data support that the CPT test may be a useful screening tool for diabetic polyneuropathy when no abnormalities are found in routine NCS.

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