Mapping Diabetic Sensory Neuropathy by Current Perception Threshold Testing

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Detailed clinical neurological examinations were conducted on 44 nondiabetic volunteers and 59 diabetic subjects. The examinations focused particularly on sensory symptomatic and physical evaluation. Standardized assessment of symptoms and physical testing of light touch, pain, vibratory, and thermal sensation was performed at the hand, wrist, elbow, foot, ankle, and knee. A total symptom score and physical score were defined by summing test scores at each site. Current perception threshold (CPT) testing that used constant sine-wave–alternating current was conducted at the same anatomic sites. CPT correlations with the physical score gave *r* values of .55 for 5 Hz, .60 for 250 Hz, and .62 for 2000 Hz (*n* = 618). Correlations with the symptom score were not as strong: *r* = .45 for 5 Hz, .46 for 250 Hz, and .51 for 2000 Hz. The correlation with symptom score was due primarily to a strong relationship for the symptom of numbness (*r* = .53 for all 3 frequencies). Correlations with pain and paresthesia were much lower. CPTs for diabetic subjects at the three frequencies were higher at most locations than for the nondiabetic volunteers. However, CPTs were no different from normal values in diabetic subjects without evidence of neuropathy. CPT testing appears to be a useful technique for assessment of diabetic sensory neuropathy. *Diabetes Care* 12:636–40, 1989

A detailed and meticulous evaluation of symptomatic complaints and loss of physical sensation is the key to diagnosis of diabetic sensory neuropathy. However, the reproducibility of the clinical examination is highly dependent on the examiner and the subject. Reliable quantitation of clinical examinations in multicenter trials of diabetic neuropathy is extremely difficult. Great reliance has been placed on nerve conduction testing to furnish comparative measures in diabetic neuropathy trials. However, sensory and motor nerve conduction velocities, response amplitudes, and latencies are dominated by large rapidly conducting myelinated fibers in nerve fascicles (1). Conversely, diabetic neuropathy involves the entire range of nerve fibers of varying diameter (2–6).The degree of correlation between nerve conduction test measures and clinically observable parameters is not strong enough to permit conclusions to be drawn from results on any single nerve (7). Even multiple nerve testing does not improve correlations to the degree optimal for serial quantitation of diabetic sensory neuropathy in clinical trials (8). Therefore, there has been considerable effort to develop techniques to enhance correspondence with clinically observable parameters. Most of these techniques include devices that attempt to standardize the customary clinical testing of vibration, light touch, pinprick, and thermal sensation (7,9–13). However, these techniques have provided correlations with clinical parameters essentially no better than those of nerve conduction testing (7,10).

We pursued measurement of the threshold of cutaneous perception of constant sine-wave–alternating current as a discriminant of diabetic sensory neuropathy. In preliminary studies, we have shown that testing at two sites (finger and toe) differentiates among several levels of clinically observable severity (14,15). Furthermore, we have demonstrated that current perception threshold (CPT) testing at the two sites correlates better with clinical measures than vibration perception thresholds (biothesiometer) or nerve conduction velocities (16).

This study was designed to extend the previous ob-

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servations. A particular goal was to expand the number of anatomic locations tested to see if CPTs could serve as a mapping procedure in surveying the extent of sensory neuropathy. Diabetic sensory neuropathy is usually worse distally, often manifesting classic stocking-glove distribution. By extending testing to proximal and distal sites, it could be determined if CPTs would reflect this clinical distribution as determined by a standard neurological examination (as conducted in the physician's office) assessing pinprick, light touch, vibration, and thermal sensation.

RESEARCH DESIGN AND METHODS

Diabetic patients not selected as to presence of neuropathy and nondiabetic control subjects with no neuropathy comprised the test population. Patients were screened for other potential sources of metabolic, toxic, traumatic or other neuropathy (e.g., alcoholism), or the recent introduction of agents affecting neuropathic evaluation (e.g., phenytoin or phenothiazines). Two patients were excluded for alcoholism, one for multiple sclerosis, and another for stroke.

All subjects underwent a complete history and physical examination and a detailed neurological symptomatic evaluation performed by the same examiner. The examiner had no knowledge of the results of the CPT testing that was performed by a different examiner. Symptoms were categorized into three separate classes: *1*) pain (subjective perception of pain described as shooting, burning, aching, tenderness, muscular, stinging, or other), *2*) paresthesia (subjective dysesthesia described as tingling, coldness, prickling, pins and needles, or other), and *3*) numbness or anesthesia (subjective recognition of lack of perception without feeling of discomfort). Patients were asked to describe each symptom as either none, mild, moderate, severe, or very severe at four sites: *1*) feet (below the ankle), *2*) legs (above the ankle to the knee), *3*) hands (below the wrist), and *4*) arms (above the wrist to the elbow). A final grade was then assigned at each site based on the self-evaluation and independent examiner assessment with these factors: none = 0, absence of symptom; mild = 1, patient does not volunteer symptom, admits to symptom only on careful questioning, not disturbed by symptom, symptom usually intermittent); moderate = 2, patient aware of symptom, disturbed by symptom (but not greatly), symptom relatively constant; severe = 3, patient very disturbed by symptom, evidence of interference in normal activities of daily living; and very severe = 4, profound disturbance and interference in normal activities. Questions used by the examiner to help evaluate the degree of severity included:

- Does the symptom wake you at night?
- Do you have to use pain pills to relieve the symptoms? What kind of pain pills?
- Can you tolerate touch such as bedsheets or wearing shoes?
- Do you burn yourself frequently because you cannot feel?
- Have you cut or otherwise injured yourself and been unable to feel it?
- Do you have difficulty buttoning your clothes or doing other fine movements because you cannot feel the buttons?
- Do you have difficulty walking in the dark because you cannot feel your feet?

The sum of the grades for the symptoms pain, paresthesia, and numbness was totaled at each site on the patient's left side and defined as the symptom score for that site. Each patient then underwent a detailed neurological physical examination focusing on the sensory examination: *1*) sensation of light touch (wisp of cotton), *2*) pinprick sensation, *3*) thermal (cold metal), and *4*) vibration (tuning fork). The test locations chosen for light touch, pinprick, and thermal were the *1*) dorsal surface of the distal phalange of the index finger, *2*) ventral surface of the wrist in the midline, *3*) ventral surface of the elbow, *4*) extensor surface of the distal phalange of the great toe, *5*) extensor surface of the ankle at the midline, and *6*) extensor surface of the leg 2 cm below the knee in the midline. Sites for vibration testing were the *1*) dorsal surface of the distal phalange of the index finger, *2*) wrist at the promontory of the radius, *3*) tip of the elbow, *4*) extensor surface of the distal phalange of the great toe, *5*) medial malleolus, and *6*) patella.

Clinical sensory testing was performed bilaterally requiring essential symmetry. One patient with significant asymmetry on physical testing was excluded from the study. Responses were graded at each site on the patient's left side for each sensory modality as: complete absence of perception, 4; minimal ability to perceive sensation, 3; ability to perceive sensation moderately impaired, 2; ability to perceive sensation mildly impaired, 1; and completely normal sensation, 0. The sum of the grades for the four sensory modalities at each site was defined as the physical score.

CPT testing. This was performed as previously described with a portable battery-operated (6-V) transcutaneous nerve stimulator (Neurometer, Neurotron, Baltimore, MD) by an examiner blinded to the clinical neurological examination results (14–16). The device emits a graded sinusoidal alternating-current stimulus at 5, 250, and 2000 Hz (cps) at intensities from 0 to a maximal level of 10 mA maintained at a constant current by feedback circuits, regardless of applied impedance. The stimulation sites were identical to those used for light touch, pinprick, and thermal physical testing on the patient's left side. The coefficient of variation of the technique on repeated measures was 5–10% depending on location (15).

Statistical analysis. Comparisons were performed with standard analysis of variance and nonparametric analysis of variance (Kruskal-Wallis) techniques (17). Associations among parameters were established with multivariate regression. Fisher's z transformation was used to assess comparative significance of various correlation coefficients.

RESULTS

Forty-four nondiabetic subjects and 59 diabetic subjects were evaluated. The control group included 28 men and 16 women, and the mean ± SE age was 39 ± 2 yr. The diabetic group consisted of 35 men and 23 women, and the mean age was 44 ± 2 yr. There were 51 insulin-dependent and 8 non-insulin-dependent diabetic subjects. Average duration of diabetes was 15 ± 1 yr, and average glycosylated hemoglobin was 11.2 ± 0.4%. The severity of neuropathy in the diabetic group was greater on the lower than the upper extremity (Fig. 1). The mean symptom scores totaled over the three sites on the upper extremity was 0.5 ± 0.1 compared to 2.3 ± 0.4 summed over the three sites on the lower extremity ($P < .05$), whereas the summed physical scores were 6.6 ± 0.9 on the upper extremity and 14.1 ± 1.8 on the lower extremity ($P < .01$).

Comparison of the diabetic group with the nondiabetic group showed higher thresholds at most sites and most frequencies in the diabetic group (Fig. 2). CPTs were significantly higher for diabetic subjects at all lower-extremity sites. On the upper extremity, all comparisons (except for the 5-Hz threshold on the finger and 5- and 250-Hz thresholds on the elbow) showed significantly higher thresholds in the diabetic subjects.

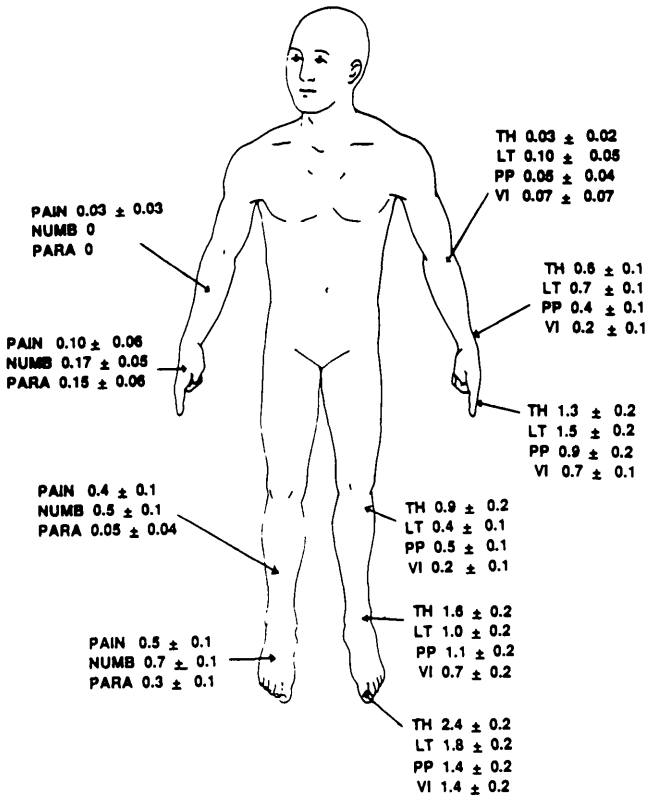

FIG. 1. Clinical exam on diabetic group. Symptoms were graded 0, normal; 1, mild; 2, moderate; 3, severe; and 4, very severe. Physical examination components were graded 0, normal perception; 1, mild absence of perception; 2, moderate absence of perception; 3, minimal perception; and 4, total absence of perception. Values are means ± SE. TH, thermal; LT, light touch; PP, pinprick; VI, vibration.

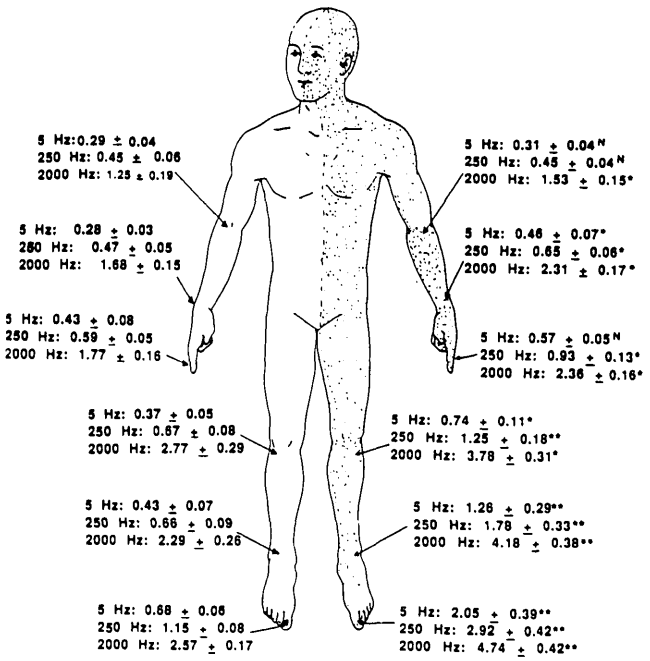

FIG. 2. Thresholds compared in diabetic and control subjects. Values for diabetic subjects are represented on *shaded* portion of body image. Values for nondiabetic control subjects are represented on *unshaded* portion. Values are given in milliamperes (mean ± SE). [N]No significant difference. *$P < .05$; **$P < .01$.

Using multivariate analysis, we found no significant age effect in our nondiabetic group, which was in agreement with our previous studies showing minimal changes in thresholds with increasing age (15). Excluding diabetic subjects ≥60 yr of age in the analysis of current data did not materially change the significant comparisons obtained. To show that the higher thresholds in diabetic subjects were due to neuropathy rather than to some nonspecific attribute of the diabetic state, it was necessary to contrast CPTs in diabetic subjects with and without neuropathy. The absence of neuropathy on either the upper or lower extremity was defined as total absence of both symptoms and physical abnormality on that extremity with a total symptom score and a total physical score of 0. To conclusively document neuropathy, we required both the presence of symptoms and physical findings. To avoid any ambiguity, the presence of either but not both symptoms or physical findings was not accepted as sufficient evidence of neuropathy in this analysis. Therefore, the contrast group was defined as both a minimum symptom score and a minimum physical score of 1 on the given extremity. Defined in this way, there were 16 patients with and 13 patients without upper-extremity neuropathy. On the lower extremity, 35 patients had neuropathy and 10 did not. Comparison of the subgroups showed sig-

nificantly higher thresholds at most sites and frequencies in the subgroups with neuropathy (Fig. 3). Furthermore, there were minimal if any differences in CPTs between diabetic subjects without neuropathy and the nondiabetic control subjects (none of the comparisons attained statistical significance).

Correlation analysis was performed between CPTs and symptom and physical scores over the entire range of sites, including both diabetic and nondiabetic subjects. CPTs at the various sites have different normal ranges. To overcome this difference in the overall correlation analysis, CPT values at each frequency at each site were expressed as the number of standard error bars above the normal range for that site. Multivariate analysis was then performed with the symptom score, physical score, and transformed CPT value at each site as the variables for the six sites and all subjects. As expected, symptom score and physical score were highly correlated (r = .66, n = 618). Correlations between CPTs and physical score (5 Hz, r = .55; 250 Hz, r = .60; and 2000 Hz, r = .62) were stronger ($P < .05$) than the corresponding correlations between CPTs and symptom score (5 Hz, r = .45; 250 Hz, r = .46; and 2000 Hz, r = .51). The multiple correlation coefficient of the three frequencies with symptom score and physical score was .53 and .65, respectively ($P < .05$). All r values were significant at $P < .001$. Additional multiple correlation coefficients were computed between the three CPT frequencies and the separate components of the symptom score and physical score. This analysis demonstrated that CPTs correlated better with numbness (r = .58) than with pain (r = .29) or paresthesia (r = .24). Vibratory sensation correlated better with CPTs (multiple r = .61) than did thermal sensation (r = .54, $P < .05$), with pinprick (r = .57) and light touch (r = .59) in between.

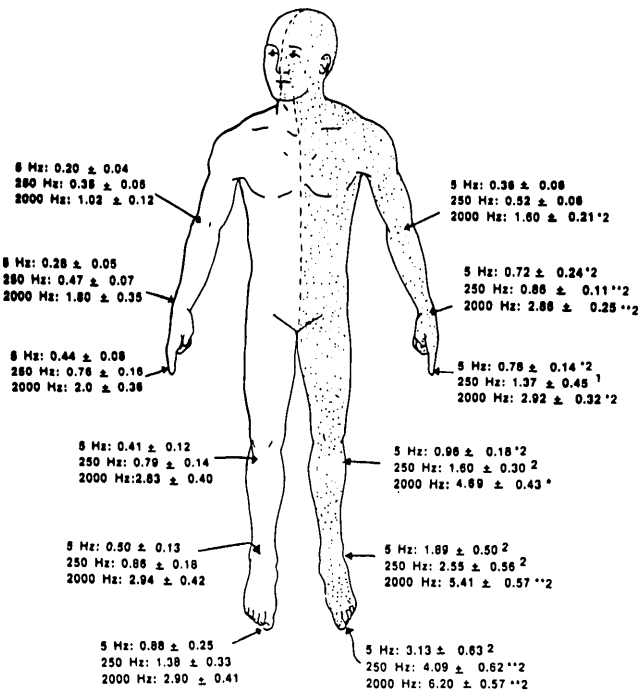

FIG. 3. Thresholds compared in diabetic subjects with and without neuropathy. Values for diabetic subjects with neuropathy are represented on *shaded* portion of body image. Values for diabetic patients without neuropathy are represented on *unshaded* portion. Values are given in milliamperes (mean ± SE). [N]No significant difference between diabetic values with and without neuropathy. *Significant difference between diabetic values with and without neuropathy ($P < .05$). **Significant difference between diabetic values with and without neuropathy ($P < .01$). [1]Significantly different from nondiabetic values ($P < .05$). [2]Significantly different from nondiabetic values ($P < .01$).

DISCUSSION

In this study, CPTs have been shown to correlate well with clinically observable parameters of diabetic sensory neuropathy. CPTs are increased significantly in diabetic subjects with neuropathy. Diabetic subjects without clinical evidence of neuropathy have CPTs similar to those of nondiabetic control subjects. The pattern of CPT increase parallels that of the clinical stocking-glove distribution. Thus, CPTs can be used to quantitatively map sensory neuropathy. CPTs are a stronger measure of objective sensory loss than of subjective indicators of neuropathy. Symptoms of pain and paresthesia correlate less significantly with CPTs than does the perception of numbness. Thus, the technique appears to have its greatest specificity in detecting nonfunctional neurons responsible for anesthesia rather than dysfunctional neurons producing symptoms of pain or paresthesia.

Our findings are of great significance for the design of clinical trials of agents, such as aldose reductase inhibitors, that affect diabetic sensory neuropathy. In this study, with a combined diabetic and nondiabetic population, we found stronger correlations of CPTs with standard clinical examination procedures than those previously reported for techniques relying on standardized devices for assessing the usual sensory modalities, such as vibration and thermal perception, with exclusively diabetic populations (7,10). This confirms our previous study in an exclusively diabetic population showing that distal CPT measures provide superior correlations to nerve conduction velocities and vibration thresholds (16). Herein we have gone further in showing that CPT changes have anatomic site specificity. Changes in clinical status in neuropathy trials might be expected to proceed along the same anatomic distribution as the neuropathy. Therefore, it is critical that CPTs reflect that same proximal-distal distribution. It is also essential that CPTs not be overly sensitive to the diabetic state as opposed to the neurological status.

We demonstrated that diabetic limbs not affected by neuropathy have CPTs similar to those of nondiabetic control subjects. CPT testing appears to be a useful tech-

nique for assessment of diabetic sensory neuropathy and should prove valuable for serial quantitation of neuropathy in clinical trials.

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