Validation of a Novel Point-of-Care Nerve Conduction Device for the Detection of Diabetic Sensorimotor Polyneuropathy

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OBJECTIVE — The diagnosis of diabetic sensorimotor polyneuropathy using objective electrophysiological tests is hindered by limited access to the specialized laboratories and technicians that perform and interpret them. We evaluated the performance characteristics of a novel portable and automated point-of-care nerve conduction study device, which can be operated by nontechnical personnel, and compared it with conventional nerve conduction studies performed in a specialist setting.

RESEARCH DESIGN AND METHODS — Seventy-two consecutive patients with diabetes (8 type 1, 64 type 2) from a diabetes and a neuropathy outpatient clinic were evaluated concurrently with conventional nerve conduction studies (the reference standard) and the point-of-care device for sural nerve function (sural nerve amplitude potentials in microvolts [μV]).

RESULTS — Sural nerve amplitude potentials measured by the point-of-care device shared very strong correlation with the reference standard (Spearman's correlation coefficient 0.95, $P < 0.001$). The Bland and Altman method yielded agreement despite a small systematic underestimation by the point-of-care device of 1.2 ± 3.4 μV. Despite this small systematic bias, the sensitivity and specificity of normal and abnormal sural nerve amplitude potentials measured by the point-of-care device for the detection of diabetic sensorimotor polyneuropathy defined by standard clinical and electrophysiological criteria were 92 and 82%, respectively.

CONCLUSIONS — A novel point-of-care device has excellent diagnostic accuracy for detecting electrophysiological abnormality in the sural nerve of patients who have diabetes. This automated device represents an alternative to conventional nerve conduction studies for the diagnosis of diabetic sensorimotor polyneuropathy.

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Diabetic sensorimotor polyneuropathy is by far the most common neurological complication of diabetes, as it imparts a lifetime risk of up to 50% (1,2). It represents an insidious and progressive process that begins with a long asymptomatic stage during which identification and management is challenging (3,4). It is important to identify neuropathy early in the course of its development, even in the asymptomatic stages, because the disease process predictably progresses to produce extreme morbidity (2,5) and health care costs (6,7) that arise from pain, imbalance, foot deformity, and the late-stage consequences of infection, ulceration, and amputation. Many of these consequences are thought to be preventable if appropriate clinical management (the combination of early identification, intensification of glycemic control, and surveillance for foot complications) is instituted (8–10).

Clinical practice guidelines for the care of people who have diabetes recommend annual screening for diabetic sensorimotor polyneuropathy using simple tools such as the 10-g Semmes-Weinstein monofilament or the 128-Hz vibration tuning fork (11,12). These simple tests predict the presence of neuropathy defined by electrophysiological criteria (nerve conduction studies) with a high level of accuracy (13). However, in many cases, such as an atypical or advanced clinical presentation, further objective testing is required. The most accurate option for further evaluation is the conventional nerve conduction study protocol conducted in specialized accredited electromyography laboratories (14). Universal nerve conduction study testing for suspected cases of diabetic sensorimotor polyneuropathy is not feasible, however, because of the limitation of such specialized resources in the face of the large diabetes population (15).

Automated electrophysiological devices (developed by Neurometrix [Waltham, MA]) that operate on the same principles as the conventional nerve conduction studies have been developed and validated for the evaluation of neurological disorders such as the mononeuropathies of the upper limbs (carpal tunnel syndrome) and the lower limbs (lumbosacaral nerve root compression, peroneal neuropathy) (16,17). The equipment consists of a portable device and disposable flexible panels that are applied to the limbs. The panels contain a preconfigured array of electrodes, thereby eliminating the need for accurate placement of individual electrodes; this accurate placement is difficult and would require the experience of a trained electromyography technologist. Rather, the testing protocol begins with an automated search for the best-situated electrode among the array that identifies the clearest measurement signal. Once the testing protocol is completed, the portable device is placed on a telemetry cable, which sends the information to a centralized analysis lab. A report is then faxed back to the clinician with the summary of results and a computer analysis. Thus, this point-of-care technology may be applied in nonspecialized set-

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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tings, such as a primary care office or a diabetes clinic, and may be operated by personnel who have minimal training in nerve conduction study techniques (18).

Although diabetic sensorimotor polyneuropathy eventually involves the diffuse disturbance of motor, sensory, and autonomic nerves, the earliest peripheral manifestation of the disease is the symmetrical impairment of the sensory axons in the longest nerve fibers (19–21). This early process is conceptually best represented by the measurement of amplitude potentials (indicative of axonal function) in the sural nerve at the region of the ankle. A point-of-care device (NC-stat; Neurometrix [http://www.neurometrix.com]) has been designed to measure the sural nerve amplitude potential as a means of quantifying such impairment in nerve axon function. We conducted a cross-sectional analysis to evaluate the validity of this newly developed point-of-care method for the assessment of sural nerve function by comparing these results with those of conventional nerve conduction studies (the reference standard) carried out in a specialized electrodiagnostic lab. Furthermore, we evaluated the accuracy of the point-of-care device for identifying the presence or absence of diabetic sensorimotor polyneuropathy, as determined by recognized clinical and electrophysiological criteria.

RESEARCH DESIGN AND METHODS

— Participants were accrued from the Diabetes Clinic and the Diabetic Neuropathy Research Clinic at the Toronto General Hospital site of the University Health Network during January to June 2005. The study protocol and consent procedures were approved by the institutional research ethics board, and written informed consent was obtained from all participants.

Consecutive patients who attended the clinics were identified and categorized for the presence or absence of diabetic sensorimotor polyneuropathy using a clinical examination and conventional nerve conduction studies. Patients were enrolled if they were at least 18 years of age and had a diagnosis of diabetes by Canadian Diabetes Association criteria (22) but were excluded from the study if anatomical changes such as limb deformity, open skin lesions, injuries, or amputation precluded appropriate placement of nerve conduction equipment electrodes. A total of 72 participants were considered for analysis because they completed both conventional nerve conduction studies conducted by the electromyography technologist, as well as the point-of-care nerve conduction studies performed by nontechnologist research staff.

Independent, masked observers performed both conventional and point-of-care nerve conduction studies during the same visit. The primary efficacy parameter for the study was comparison of nerve conduction in the sural nerve between these two methods. However, because we also aimed to compare the presence of abnormality in the sural nerve by the point-of-care device with the overall presence or absence of diabetic sensorimotor polyneuropathy, patients underwent a full clinical examination as well as full upper- and lower-limb conventional nerve conduction studies to classify their neuropathy status by the American Academy of Neurology criteria (described below) (14). The order of testing was random and interpretation of the results was masked.

Conventional nerve conduction studies (the reference standard)

Standardized procedures with the Counterpoint device (Medtronic, Mississauga, Canada) were used to measure nerve conduction according to the standards of the American Association for Neuromuscular and Electrodiagnostic Medicine and the Canadian Society of Clinical Neurophysiology. In accordance with these standards, lower-limb temperature was maintained at a minimum of 31.0°C and upper-limb temperature at a minimum of 32.0°C for the duration of the testing. Standard surface-stimulating and -recording techniques with fixed distances were used. Measurements of latencies, distances, and amplitudes were done in a standard fashion using onset latencies and baseline-to-peak amplitudes; for sensory curves, initial positive peak–to–negative peak measurements were made. The Counterpoint equipment calculated conduction velocities automatically. In addition to measuring the sural nerve sensory amplitude for the purpose of the primary efficacy parameter, to classify the status of clinical polyneuropathy, the nondominant median motor and sensory nerves and the dominant peroneal nerves were also tested. All sensory nerve conduction studies were antidromic. Low interobserver and intraobserver variability have been observed for these measurements using the techniques described (20). Based on the commonly accepted criteria of the American Academy of Neurology, classification of diabetic sensorimotor polyneuropathy requires the presence of one or more neuropathic symptoms or signs together with the presence of electrophysiological polyneuropathy, defined by abnormality of three or more parameters in two or more nerves (14).

Point-of-care nerve conduction studies

The point-of-care nerve conduction studies were performed using the NC-stat system, which was designed to perform standard noninvasive nerve conduction studies by nontechnical personnel. The system has four components: *1*) the biosensors, which are single-use, nerve-specific flexible panels that are applied to the patient and integrate the stimulating and sensing electrodes with a gel and a temperature sensor in a configuration that ensures correct placement even by nontechnical personnel; *2*) the monitor, which is a battery-operated device that reads and displays the data transmitted from the biosensors; *3*) the docking station, which transmits the data from the monitor; and *4*) the remote on-call information system, which analyzes the information received from the docking station and monitor by telephone lines and generates a report that is sent to the clinic by fax. An embedded chip in the biosensor panel measures skin surface temperature and either the monitor indicates that limb warming is necessary or the analysis in the remote on-call information system adjusts for this covariate. A single 1-h teaching session was held with the research staff responsible for performing the point-of-care protocol. Those staff members were not technicians and did not discuss the results of their recordings or any technical or clinical information about the study participants with the electromyography technologists who performed the conventional nerve conduction studies (the reference standard). Although biosensors are available for multiple body-site analyses, for the purposes of this study we applied only the sural nerve biosensors. The point-of-care device automatically zeros sensory nerve amplitude potential signals <2.1 μV. Application of the sural nerve biosensors and running of the protocol required ~5–6 min per subject.

Table 1—*Clinical characteristics of the 72 study participants with diabetes*

Female sex	26 (36)
Age (years)	56 ± 11
Diabetes type	
Type 1 diabetes	8 (11)
Type 2 diabetes	64 (89)
Diabetes duration (years)	12 ± 10
Diabetes therapy	
Therapeutic lifestyle change alone	6 (8)
Oral hypoglycemic agents	47 (65)
Insulin	15 (21)
Combined oral agents and insulin	4 (6)
Current smoking	8 (11)
Height (cm)	170 ± 10
Weight (kg)	88 ± 21
Sural nerve amplitude potential (μV)†	5.6 ± 5.9
Presence of diabetic sensorimotor polyneuropathy‡	50 (69)

Data are means ± SD or *n* (%). †As measured by conventional nerve conduction studies (the reference standard). Values ≤6 μV are considered abnormal. ‡According to the commonly accepted American Academy of Neurology criteria described in RESEARCH DESIGN AND METHODS.

Statistical analysis

Descriptive statistics and analysis for correlation and agreement were performed in SAS version 8.02 for Windows (SAS Institute, Cary, NC). The sample size estimation was based on correlation between the sural nerve sensory amplitude potential by the two methods using Fisher's z-transform approach in an equivalency study design with 95% power, two-sided significance ($\alpha = 0.05$), and the conservative assumption of a worst-case correlation coefficient of 0.40. Correlation was analyzed using Spearman's correlation coefficients for all comparisons. Agreement for sural nerve amplitude potential values between conventional and point-of-care nerve conduction studies was assessed by the method of Bland and Altman (23,24). In the analysis, no attempt was made to account for the limitation of the point-of-care device at sensory nerve amplitudes below 2.1 μV. Operating characteristics for the ability of the point-of-care system to detect the presence or absence of diabetic sensorimotor polyneuropathy were based on the definition of ≤6 μV as abnormal sural nerve sensory amplitude potential.

RESULTS — A total of 72 patients were enrolled in the study. The clinical characteristics are shown in Table 1. Most patients had type 2 diabetes, and the mean age and diabetes duration were 56 ± 11 and 12 ± 10 years, respectively. As an indication of the distribution of the severity of neuropathy in this study cohort, the sural nerve amplitude potential, as measured by the conventional nerve conduction studies, was skewed to the lower values with a mean of 5.6 μV, a median of 3 μV, and an interquartile range of 1.1–9.0 μV. Of the 72 study participants, 16 (22%) had undetectable sural nerve amplitude potentials indicative of a greater neuropathy severity. In total, 50 participants (69%) met the clinical criteria for the presence of diabetic sensorimotor polyneuropathy.

All 16 participants who had undetectable sural nerve amplitudes, as measured by the conventional nerve conduction study protocol, also had undetectable measurements by the point-of-care method. However, an additional 14 participants had undetectable levels by the point-of-care method: the mean sural nerve amplitude potential by the reference method in these individuals was 2.1 μV, with a maximal value of 3.8 μV. Although the amplitude potential was measurable by the reference method in these individuals without a measurable point-of-care response, all of these values are conventionally considered to be abnormally low by clinical standards. This finding is explained in part by an automatic standardization of the point-of-care device, which automatically assigns a measurement of zero microvolts for levels <2.1 μV (see RESEARCH DESIGN AND METHODS). Correlation between the sural nerve amplitude potentials for the conventional and the point-of-care nerve conduction studies was high, such that the Pearson correlation coefficient was 0.95 ($P < 0.001$) (Fig. 1). The plotted regression line in Fig. 1 suggests that there is a small magnitude of bias such that the point-of-care method may systematically underestimate the sural nerve amplitude potential measured by the reference method, which is in part explained by the lack of signal detection by the point-of-care device at levels <2.1 μV.

To further explore the positive correlation between the methods and to better quantify the systematic bias, we applied the statistical method of Bland and Altman. Figure 2 demonstrates the difference between sural nerve amplitude

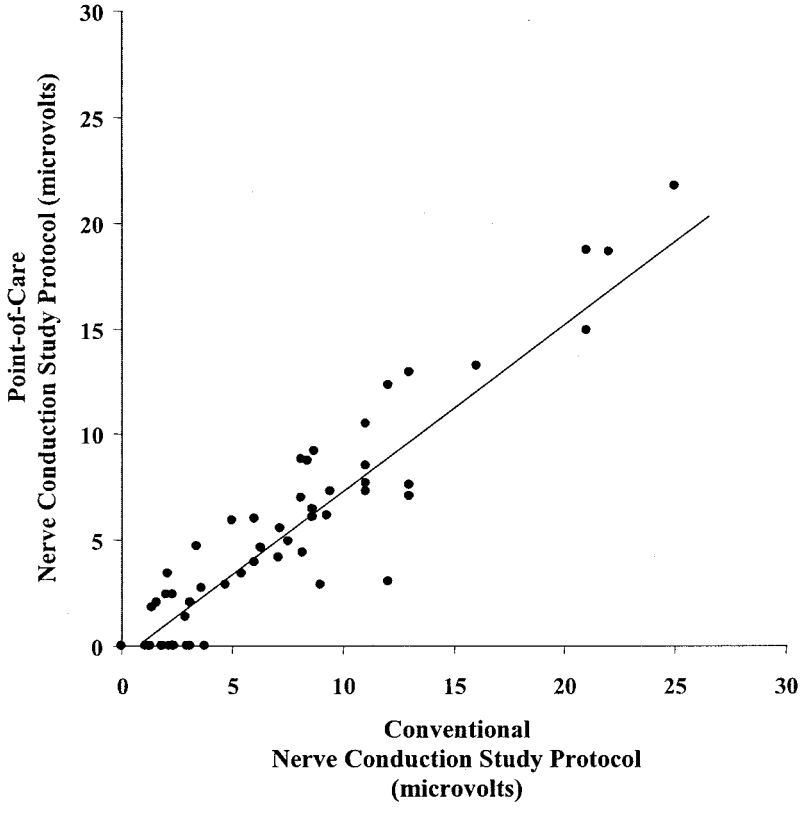

Figure 1—*Correlation between sural nerve amplitude potentials obtained by the conventional and point-of-care nerve conduction study protocols in the 72 participants who had diabetes. *Spearman correlation coefficient = 0.95 (P < 0.0001).*

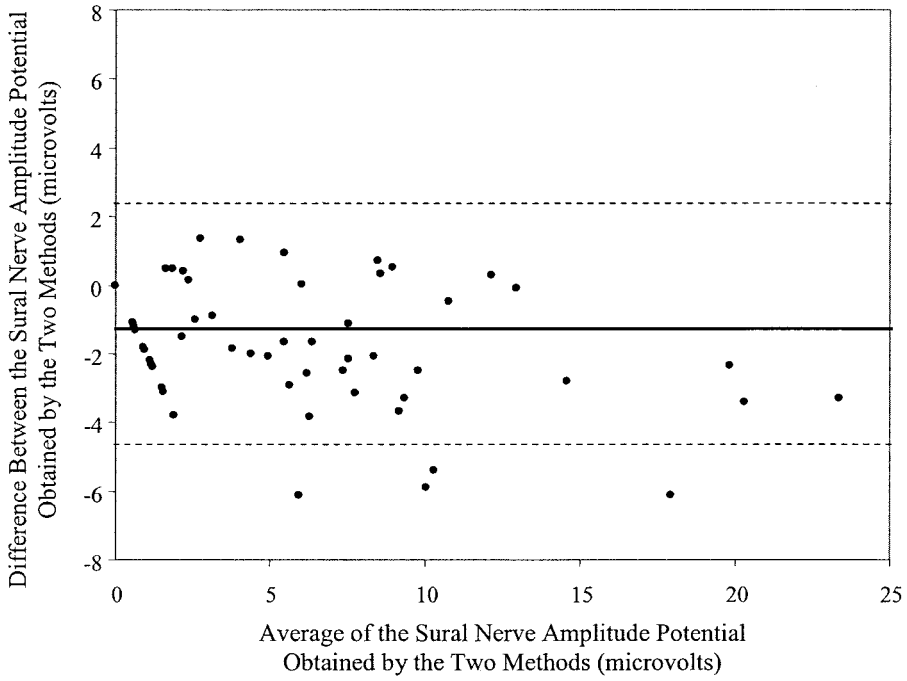

Figure 2—*Agreement between sural nerve amplitude potentials for the conventional and the point-of-care nerve conduction studies in the 72 participants who had diabetes. "Agreement" refers to the difference plotted against the mean of the sural nerve amplitude potentials by the two methods. This comparison uses the Bland and Altman method (15,16) described in* RESEARCH DESIGN AND METHODS*. The broken lines represent the upper and lower critical values for the 95% distribution in the difference between the sural nerve potential amplitudes obtained by the two methods (threshold obtained by the point-of-care protocol minus that obtained by the conventional nerve conduction study protocol); the solid line represents the mean difference. The lower critical value is a difference of −4.6 μV and the upper critical value is a difference of +2.3 μV. Bias is minimal, such that the mean difference is −1.2 μV for the point-of-care protocol minus that of the conventional nerve conduction study.*

potentials (point-of-care method minus the conventional method of nerve conduction study) plotted against the average sural nerve amplitude potential between the two methods. Figure 2 demonstrates strong quantitative agreement between the two methods across the full range of average values. However, a small systematic bias is observed, such that the point-of-care device underestimates the reference sural nerve potential amplitude value by an average of 1.2 μV compared with the measurement made by the referent method. This pattern did not change when the analysis was repeated with log-transformed values (data not shown).

Based on our observations, we went on to explore whether abnormality in the sural nerve sensory amplitude as measured by the point-of-care protocol would be associated with the presence or absence of diabetic sensorimotor polyneuropathy, as defined by clinical and conventional electrophysiological evaluation. We defined abnormality in the sural nerve amplitude potential determined by the point-of-care device as ≤6 μV, based on conventional criteria. The sensitivity and specificity of the point-of-care device for the detection of polyneuropathy by this criterion was 92 and 82%, respectively. The positive and negative predictive values were also 92 and 82%, respectively. The overall accuracy of this method, defined as the measure of true findings (sum of the true-positive and true-negative results) divided by all test results, was 89%.

The median time between the application of the point-of-care system biosensors to the patients' ankles and the time when the final report and computer analysis were received by fax was 40 min (interquartile range 20–79).

CONCLUSIONS — This study demonstrates that a point-of-care device can accurately measure the earliest peripheral manifestation of diabetic sensorimotor polyneuropathy (i.e., abnormality in the sural nerve sensory amplitude) by non-technologist staff in a nonspecialized clinical setting. Measurements of the amplitude potential obtained using a point-of-care device agree with measurements obtained by using the conventional method performed by electromyography technicians, with a minimal average bias of 1.2 ± 3.4 μV. As a secondary analysis, we explored the nature of this bias and found that it does not appear to be clinically important. Specifically, abnormality of the sural nerve amplitude potential as measured by the point-of-care device detects the presence of polyneuropathy (as determined by clinical and diffuse electrophysiological criteria interpreted by a specialized neurologist) with acceptable sensitivity and specificity.

Conventional nerve conduction studies performed in a specialist setting are considered to be the most reliable, accurate, and sensitive measure of peripheral nerve function and are believed to be an essential component of the accurate diagnosis of diabetic sensorimotor polyneuropathy (14). However, the present standards of clinical practice place responsibility for the management of diabetes and screening for complications in the hands of the primary care practitioner or the diabetes specialist. According to clinical practice guidelines, screening for diabetic sensorimotor polyneuropathy is done using simple sensory tools such as the 10-g Semmes-Weinstein monofilament or the 128-Hz vibration tuning fork (11,12). Symmetrical sensory loss is consistent with polyneuropathy and warrants the exclusion of sensory loss from familial, toxic, alcoholic, and uremic causes or from vitamin deficiencies. However, if sensory loss is asymmetrical or occurs in patients who have a short duration of diabetes or with chronic glycemic control at target levels, further investigation by a neurologist is warranted. Thus, a valid quantitative tool to assess the presence and severity of diabetic sensorimotor polyneuropathy in a primary care or diabetes clinic setting could play an important role in the management of patients who have diabetes and could preclude the need for referral to a specialized clinical neuropathy laboratory.

The results of this study demonstrate that the measurement of sural nerve amplitude potentials is sufficiently accurate for use in clinical research protocols. The small systematic bias is in part explained by the lack of signal detection for extremely low levels of sural nerve sensory amplitude by the point-of-care device for levels <2.1 μV. Normal responses, al-

though often standardized for age, are generally considered to be >6 μV.

Although the results of our study suggest that a clinical approach that permits the diagnosis of diabetic sensorimotor polyneuropathy in a primary care or diabetes clinic setting may be feasible, there are potential limitations. First, the objective of this study was to compare the sural nerve amplitude potential measured by the point-of-care system with the conventional method of nerve conduction studies in a broad spectrum of patients. Thus, further study is needed of patients who present with atypical neuropathy in a clinical setting. Further investigation is also needed into specific approaches that include the point-of-care nerve conduction study method as a fundamental component of the clinical protocol for the diagnosis of polyneuropathy. Finally, the ability to apply this method in the context of clinical visits for usual diabetes follow-up, and the short turn-around time between testing and the receipt of an interpretation, is consistent with the philosophy of efficient, patient-centered care. However, the cost-effectiveness of this approach needs to be studied before the widespread application of this diagnostic technology in diabetes care.

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