Cooling Detection Thresholds in the Assessment of Diabetic Sensory Polyneuropathy

Comparison of CASE IV and Medoc instruments

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OBJECTIVE — Cooling detection threshold testing may be an important quantitative method for assessing polyneuropathy, in that it has traditionally been viewed as a measure of small-fiber involvement. The present study sought to determine the agreement between two common testing devices and to determine whether these are concordant in their association with predictor variables for diabetic sensory polyneuropathy.

RESEARCH DESIGN AND METHODS — A total of 83 patients with diabetes (10 patients with type 1 diabetes and 73 patients with type 2 diabetes) and a wide spectrum of diabetic sensory polyneuropathy severity underwent concurrent cooling detection threshold testing using the Medoc and CASE IV instruments. Common predictor variables for diabetic sensory polyneuropathy were measured on the same day.

RESULTS — Measurements of cooling detection thresholds by both instruments were highly correlated (Spearman’s correlation coefficient 0.81, \( P < 0.001 \)) and demonstrated a high degree of agreement by the method of Bland and Altman (95% distribution critical values for the difference in cooling detection thresholds, +7.5 and −5.6°C). Cooling detection thresholds by both instruments were strongly correlated with clinical indicators of large-fiber neuropathy but not with the symptoms of small-fiber neuropathy (pain).

CONCLUSIONS — These two instruments available for assessment of cooling detection thresholds are interchangeable for research in diabetic sensory polyneuropathy. However, this modality is equivalent to other modalities of quantitative sensory threshold testing in its association with indicators of large-fiber neuropathy and does not seem to provide an advantage for the prediction of small-fiber involvement.

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Quantitative sensory threshold testing is an important noninvasive tool for the investigation of diabetic sensory polyneuropathy and, as a consequence, is commonly used in clinical trials (1–5). Quantitative sensory threshold tests are capable of assessing individual sensory modalities, including the perception thresholds for vibration and thermal stimuli. A number of different devices are used in clinical practice and in research, but the manner in which results from these devices relate to each other for a given modality is frequently speculative.

Vibration perception threshold testing is the quantitative modality most commonly used for assessment of diabetic sensory polyneuropathy. Results are believed to represent large fiber sensory nerve function because of evidence for strong associations with sural nerve action potential amplitude (6) and with clinical measures of large fiber function (7). For this modality, it has also been demonstrated that two different devices displayed strong correlation and agreement with each other in the measurement of vibration perception thresholds (7). However, for thermal detection thresholds, the different devices have not been systematically compared (4,8–10). This is of paramount importance, in that thermal detection thresholds (cold and heat detection) have the major theoretical advantage of specifically representing small-fiber sensory nerve function (11,12).

Studies that aim to explore the natural history and potential treatment of small-fiber neuropathy using thermal detection threshold testing must ensure that the available devices are measuring the same biology of nerve function and structure. In this regard, it is essential to establish whether assumptions made about nerve structure and function from one device are generalizable to another device.

To test this issue, we assessed the correlation and agreement between cooling detection thresholds obtained at the same anatomic site in patients with diabetic sensory polyneuropathy using the two common testing devices: the Medoc instrument and the CASE IV instrument.

RESEARCH DESIGN AND METHODS — The study was conducted at the Toronto General Hospital/University Health Network (TGH/UHN) in the Diabetic Neuropathy Research Clinic from June 2002 to January 2003. Approval from the University Health Net...
Table 1—Clinical stratification method using the Toronto Clinical Neuropathy Score

<table>
<thead>
<tr>
<th>Symptom scores</th>
<th>Reflex scores</th>
<th>Sensory test scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot pain</td>
<td>Knee reflexes</td>
<td>Pinprick</td>
</tr>
<tr>
<td>Numbness</td>
<td>Ankle reflexes</td>
<td>Temperature</td>
</tr>
<tr>
<td>Tingling</td>
<td></td>
<td>Light touch</td>
</tr>
<tr>
<td>Weakness</td>
<td></td>
<td>Vibration</td>
</tr>
<tr>
<td>Ataxia</td>
<td></td>
<td>Position sense</td>
</tr>
</tbody>
</table>

Upper limb symptoms

Symptom scores were graded as present = 1, absent = 0 (numbness, tingling as perceived at toes and in feet). Reflex scores were graded as absent = 2, reduced = 1, normal = 0 for each side. Sensory test scores were graded as abnormal = 1, normal = 0. Maximum possible score was 19. The score was used to stratify patients into three groups of severity: 6–8 indicated mild neuropathy, 9–11 indicated moderate neuropathy, and ≥12 indicated severe neuropathy.

were identified and categorized using the Toronto Clinical Neuropathy Score (13) (Table 1). The Toronto Clinical Neuropathy Score was used to stratify patients into three groups of diabetic sensory polyneuropathy severity: 6–8 indicated mild neuropathy, 9–11 indicated moderate neuropathy, and ≥12 indicated severe neuropathy. Study accrual was terminated when the smallest group consisted of 25 study subjects. A total of 83 participants were considered for analysis because they completed the cooling detection threshold testing component of the study protocol. All patients first underwent a comprehensive medical and neurologic evaluation to exclude neuropathy secondary to etiologies other than diabetic sensory polyneuropathy (e.g., alcohol, uremia, nutritional deficiency, toxins, familial neuropathy). The clinical characteristics of the 11 patients who did not complete the protocol did not differ significantly from those of the 83 participants (data not shown).

Study protocol

Cooling detection thresholds were obtained on the dorsum of the left foot using the Medoc TSA-II NeuroSensory Analyzer (Ramat-Yishai, Israel) and the CASE IV instrument (WR Electronics, Minneapolis, MN). Cooling detection threshold testing was performed on each patient using both the Medoc and CASE IV devices using a random selection of the order of testing. The stimulus was applied to the dorsum of the left foot, and both devices were used during the same clinical visit within a 4-h interval. To eliminate observer bias, a different technician operated each device for each patient.

The Medoc device used a method of limits (9). The stimulus was applied to the dorsum of the foot at a temperature of 32°C, and the temperature was gradually decreased to the first level detected by the patient as a cooler stimulus than the preceding. Five trials were performed, and a catch trial, with null stimulus, was inserted randomly during testing. An average of the five levels was taken.

Testing with the CASE IV device was performed using the 4–2–1 testing algorithm (14). The stimulator was applied to the dorsum of the left foot. The stimulus range was in 25 preprogrammed steps from 0 (no stimulus/warmest temperature) to 25 (maximum stimulus/coldest temperature). The starting point for testing was at point 13 (midpoint of the range), which was at a preset baseline temperature of 30°C. If the patient perceived the stimulus as cold, then the temperature was increased by four steps. If still perceived as cold, then the temperature was increased by another four steps. If the stimulus was not perceived as cold at the higher temperature, then the temperature was lowered by two steps. If perceived as cold, it was increased by one step. When the patient could not distinguish between two levels separated by the lowest step of 1, then that level was defined as the just-noticeable-difference (JND) for cooling perception. Reproducibility has previously been demonstrated to be very good for cooling detection thresholds in the lower extremity by both instruments (15,16).

The CASE IV instrument does not detect cooling thresholds <9°C. To compare cooling detected at lower temperatures, an arbitrary value of 0°C was assigned for any CASE IV result of a cooling detection threshold of ≤9°C. The Medoc device can detect a cooling detection threshold as low as 0°C.

The assessment of predictor variables was conducted on the same day as the cooling detection threshold measurements. Pain assessment was determined using an 11-point Likert visual analog scale of the modified short form McGill pain questionnaire (17). Monofilament testing and nerve conduction studies of the lower limbs were each conducted separately by an individual masked to the results of all other testing. Monofilament testing was conducted to determine the number of insensate responses out of eight applications to the dorsum of the great toe bilaterally. Although a number of different techniques for monofilament testing exist, this technique has been validated as a reliable screening test for the diagnosis of diabetic neuropathy (18). Quantitative measurement of vibration perception threshold was performed with the Medoc device using the method of limits (9). Nerve conduction studies were conducted with Keypoint electrophysiology equipment (Medtronic, Mississauga, Ontario, Canada) using standardized testing of the left sural sensory nerves for signal amplitude, and temperature was maintained at >31°C in the lower extremities.

Statistical analysis

Descriptive statistics and linear regression were performed in SAS (version 8.02 for Windows; SAS Institute, Cary, NC). Agreement of the cooling detection thresholds (in °C) obtained with the two instruments was compared by the method of Bland and Altman (19,20). Correlation was analyzed using Spearman’s correlation coefficients for all comparisons, including analysis of the correlation between cooling detection thresholds and vibration perception thresholds with sural nerve sensory amplitudes. All predictor variables for the univariate linear regression models with the cooling detection threshold as dependent variable were continuous, and the linearity assumptions were confirmed by standard regression diagnostics.

RESULTS — A total of 83 patients were enrolled in the study. The clinical characteristics are shown in Table 2. Most
patients had type 2 diabetes, and the mean duration of diabetes was 10 years. Patients had a wide spectrum of diabetic sensory polyneuropathy severity and, overall, had a moderate degree of diabetic neuropathy as determined by the Toronto Clinical Neuropathy Score (mean score 10.1 ± 8.0 out of 19).

Cooling detection thresholds obtained with the Medoc instrument strongly correlate with those obtained from the CASE IV (Spearman’s correlation coefficient 0.81, \( P < 0.001 \); Fig. 1). The plotted regression line in Fig. 1 approximates the line of equality (slope of 1), and therefore no systematic bias is observed.

To further explore agreement between the variables, the statistical method of Bland and Altman (19,20) was performed. Figure 2 demonstrates the difference between cooling detection thresholds (CASE IV threshold minus Medoc threshold) plotted against the average cooling detection threshold for the two devices. Figure 2 shows very good agreement between cooling detection threshold measurements by the two devices across the full range of average values (Fig. 2). No change in the pattern seen in Fig. 2 was noted when the analysis was repeated with log-transformed values (data not shown).

Although a strong correlation between the CASE IV and Medoc instruments was observed, we aimed to confirm that the two instruments measured the same aspects of nerve structure or function by pursuing an analysis of common determinants for diabetic sensory polyneuropathy (Table 3). We hypothesized that if an association with such a risk factor was discordant between the CASE IV and the Medoc instruments, then this may indicate that the machines are not measuring the same aspects of nerve fiber biology. Clinical parameters (duration of diabetes and the Toronto Clinical Neuropathy Score), physical examination maneuvers (the monofilament score), and electrophysiologic parameters (sural nerve sensory amplitude) were all strongly associated with cooling detection threshold measured by both instruments (Table 3). Pain symptoms, traditionally believed to be a sensory modality mediated by small nerve fibers (11,12,21) were not predictive of cooling detection thresholds using either instrument. Sural nerve amplitude, a reliable marker of large sensory fiber function, had the strongest association with cooling detection thresholds (Spearman’s correlation coefficients −0.64, \( P < 0.001 \), and −0.62, \( P < 0.001 \), for the Medoc and CASE IV

**Table 2—Clinical characteristics of the 83 study participants with diabetes**

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>53 (64)</td>
</tr>
<tr>
<td>Women</td>
<td>30 (36)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.9 ± 9.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>73 (88)</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>10.1 ± 8.0 (years)</td>
</tr>
<tr>
<td>Duration of neuropathy</td>
<td>3.3 ± 3.7 (years)</td>
</tr>
<tr>
<td>Neuropathy grade*</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>32 (39)</td>
</tr>
<tr>
<td>Moderate</td>
<td>26 (31)</td>
</tr>
<tr>
<td>Severe</td>
<td>25 (30)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.6 ± 2.2%</td>
</tr>
</tbody>
</table>

Data are \( n \) (%) or means ± SD. *According to the grading system derived from the Toronto Clinical Neuropathy Score (see RESEARCH DESIGN AND METHODS section for full details).
difference of obtained by the Medoc instrument). There is very good agreement across the full range of average values, such that the upper critical value is a difference of +7.5°C and the lower critical value is a difference of −5.6°C. Bias is minimal, such that the mean difference is +1.4°C for the Case IV instrument minus that obtained by the Medoc instrument.

Both the CASE IV and Medoc protocols were tolerated well by all patients, and there were no reports of discomfort associated with either instrument.

**CONCLUSIONS** — Quantitative sensory threshold testing is an important, noninvasive tool used to quantitate the extent of peripheral nerve injury. It has become a useful parameter in clinical trials for patients with diabetic sensory polyneuropathy. Although it is assumed that different devices reliably measure the same modality, agreement between the devices must be demonstrated before comparisons can be made between studies.

Strong correlation and agreement were observed for cooling detection thresholds using the two devices in this study. The agreement was maintained across the full range of values, indicating that the severity of diabetic sensory polyneuropathy did not influence the consistency of measurement by each device. In addition, clinical parameters known to predict diabetic sensory polyneuropathy correlated strongly and concordantly with cooling detection thresholds measured by both devices. From this level of agreement and concordance, we can confidently infer that the Medoc and CASE IV

### Table 3—Univariate association of selected predictor variables on cooling detection thresholds obtained by CASE IV and the Medoc instruments

<table>
<thead>
<tr>
<th>Variable</th>
<th>CASE IV Unadjusted parameter estimate (β)*</th>
<th>P</th>
<th>Medoc Unadjusted parameter estimate (β)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.07</td>
<td>0.51</td>
<td>0.03</td>
<td>0.78</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>−0.45</td>
<td>&lt;0.001</td>
<td>−0.43</td>
<td>0.001</td>
</tr>
<tr>
<td>Pain score†</td>
<td>−0.01</td>
<td>0.98</td>
<td>−0.18</td>
<td>0.76</td>
</tr>
<tr>
<td>Toronto Clinical Neuropathy Score‡</td>
<td>−1.47</td>
<td>&lt;0.001</td>
<td>−1.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Monofilament score§</td>
<td>−1.6</td>
<td>&lt;0.001</td>
<td>−1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sural amplitude</td>
<td></td>
<td></td>
<td>0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vibration perception (μm)</td>
<td>−0.19</td>
<td>&lt;0.001</td>
<td>−0.22</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Univariate associations with cooling detection thresholds were remarkably concordant between the two methods of measurement. The relationships between HaNa and the cooling detection threshold measured by the CASE IV and Medoc instruments were strong (unadjusted β-coefficient of −0.65 (P = 0.21) and −0.94 (P = 0.07, respectively), but measurements were unavailable for 31 of the 83 participants for this variable. *Parameter estimates are for the linear regression of the continuous variables on cooling detection threshold in °C. For example, every increase in duration of diabetes by 1 year is associated with a mean decrease in the cooling detection threshold of 0.45°C for the CASE IV instrument and 0.43°C for the Medoc instrument; †the pain score is derived from a visual analog scale as described in the RESEARCH DESIGN AND METHODS section and varies between 0 (no limb pain) and 10 (maximal limb pain); ‡aggregate score of symptoms and signs described in RESEARCH DESIGN AND METHODS section. The total score ranges from 0 (no neuropathy) to 19 (severe neuropathy); §the number of insensate responses out of eight applications of the monofilament to the dorsum of the great toe bilaterally; ||the sensory amplitude potentials in the sural nerve of the left leg by electrophysiologic methods (μV).
Cooling detection thresholds in patients with diabetes

devices are representing the same sensory pathways. Whether these pathways involve large fibers exclusively or a combination of small and large fibers is a question for further study. The results of research studies that investigate the role of cooling detection thresholds to characterize the nature of diabetic sensory polyneuropathy can therefore be directly compared regardless of whether the CASE IV or the Medec instruments are used.

Although also associated with large fiber injury (21,22), pain sensation is believed to be a sensory modality mediated primarily by small-caliber nerve fibers. In this study, no correlation was demonstrated between cooling detection thresholds and pain scores measured by a quantitative visual analog scale. Although pain has traditionally been regarded as a manifestation of small-fiber function, this study is consistent with other cross-sectional (23) and prospective (24) studies in demonstrating a discordance between pain scores and small-fiber neuropathy. Supportive evidence for pain as a predictor of small-fiber structure and function remains to be demonstrated. In a recent study of nerve fiber morphology (25), a cohort of patients diagnosed with idiopathic painful small-fiber neuropathy underwent cooling detection threshold testing, nerve conduction studies, and intra-epidermal nerve fiber analysis of skin biopsy. The latter is regarded as the reference standard for the identification of small-fiber neuropathies. Intra-epidermal nerve fiber density was abnormal in 90% of patients, whereas only 60% of patients had abnormal cooling detection thresholds. Electrophysiology and vibration perception thresholds were abnormal in a significant proportion of patients with morphologic evidence for small-fiber neuropathy, indicating that large-fiber damage was present in a significant proportion despite a clinical presentation that suggested exclusive small-fiber neuropathy.

Nerve conduction studies remain the most reliable, accurate, and sensitive measure of peripheral nerve function (26). However, the technique assesses the function of large-caliber nerve fibers exclusively. It has been shown that vibration perception threshold testing using two different instruments correlated strongly with sural nerve action potential amplitudes over a wide range of diabetic sensory polyneuropathy severity (7). Akin to vibration perception thresholds, the current study has demonstrated that cooling detection thresholds are an alternate quantitative sensory threshold marker for the degree of large-fiber neuropathy as measured by sural nerve amplitudes. This finding is consistent with a study of thermal and vibration perception thresholds in the diagnosis of diabetic sensory polyneuropathy (27). Current data suggest that an intimate association exists between large- and small-fiber damage in diabetic sensory polyneuropathy and that these separate functional or structural disturbances cannot be distinguished using quantitative sensory testing in this patient population.

This study demonstrates that two cooling detection threshold instruments, the Medec and CASE IV, have strong correlation and quantitative agreement and are representing the same underlying nerve pathology. Although both devices can be used for clinical or research purposes, the Medec device may be favored in studies of moderate and severe diabetic sensory polyneuropathy because it is able to quantify cooling detection thresholds at lower temperature ranges (below 9°C) than the CASE IV instrument. In terms of the validity of cooling detection thresholds in representing the nature of nerve fiber involvement, this study failed to intimate a relationship between cooling detection thresholds and small-fiber neuropathy. Instead, cooling detection thresholds behave as reliably as vibration perception thresholds in their association with markers of large-fiber neuropathy in diabetes patients. All evidence taken together, it seems that small-fiber neuropathy is not mutually exclusive from large fiber involvement, and abnormality in the structure of small nerve fibers does not reliably predict functional deficits in these fibers in patients with diabetes. Future studies of quantitative sensory threshold testing and small-fiber morphology are required to define the role of small-fiber neuropathy in diabetic sensory polyneuropathy.

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References


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