SCRIPTA MEDICA (BRNO) –78 (3): 177–184, *August 2005*

REPRODUCIBILITY OF THERMAL THRESHOLD ASSESSMENT IN SMALL-FIBRE NEUROPATHY PATIENTS

MORAVCOVÁ E.[1], BEDNAŘÍK J.[1], SVOBODNÍK A.[2], DUŠEK L.[2]

[1]Department of Neurology, Faculty of Medicine, Masaryk University, Brno
[2]Centre for Biostatistics and Analyses, Masaryk University, Brno

Received after revision August 2005

A b s t r a c t

To evaluate the test-retest reproducibility of thermal threshold testing (TTT) in small-fibre neuropathy (SFN) patients.

Methods: Thermal thresholds for cold (CP) and warm (WP) perception were repeatedly evaluated over a period of 1 week in a group of 58 SFN patients and in 30 healthy volunteers. Thermal thresholds were established in the hand and foot using 3 different algorithms.

The coefficients of repeatability (CR) (expressed as 2 multiple of SD_{dif} calculated as $\sqrt{\sum \text{difference}^2 / n}$, where n represents the number of all measurements) varied between 0.72° and 1.5°C in the hand and between 2.2 °C and 3.7 °C in the foot in healthy volunteers and SFN patients respectively. The reproducibility of all the tests in the hand and of CP tests in the foot was higher in healthy volunteers in comparison with SFN patients. Thermal threshold values in both SFN patients and healthy volunteers showed higher reproducibility in the hand compared with those in the foot. Cold threshold values obtained from the foot in the SFN group showed lower reproducibility compared to the warm threshold ones, while the opposite difference was found in healthy subjects. The method of levels displayed higher reproducibility of cold thresholds in both groups in comparison with the method of limits.

If TTT is intended for use as a method of longitudinal assessment of small-fibre nerve function, different limits for the incidental (i.e. non-significant) intraindividual change of thermal threshold should be used for patients with and without disturbed thermal perception. The modality tested, type of the test, and tested region may well display a significant impact on the reproducibility of thermal threshold values.

K e y w o r d s

Sensory thresholds, Polyneuropathies, Reproducibility of results, Small fibre, Quantitative sensory testing

INTRODUCTION

The thermal threshold testing method (TTT) is a quantitative sensory test (QST) commonly used in the assessment of small A-δ and C-fibre function. Several published studies have addressed the comparison between various algorithms and the influence of physiological variables on the thermal threshold values (*1–5*).

Reproducibility is a major consideration when a choice between different tests has to be made, as it affects both the sensitivity and the specificity of the measurements

as well as the statistical power of clinical and epidemiological investigations (*4*). Moreover, high reproducibility is vital for longitudinal assessment of threshold changes resulting either from the natural course of the disease or through treatment. Several studies exist on the reproducibility of quantitative sensory threshold values, including thermal threshold tests (*2–10*). There are, however, only few investigations addressing the issue of the reproducibility of different testing algorithms in subjects with both normal and particularly abnormal thermal thresholds (*10,11*).

The aim of this study was to assess the reproducibility of thermal threshold assessment in patients with small-fibre neuropathy (SFN) in comparison with normal subjects, utilising different testing algorithms.

MATERIALS AND METHODS

Thermal thresholds for cold and warm perception were examined twice over a period of 1 week in 58 patients with pure or predominant small-fibre sensory polyneuropathy (37 men, 21 women, mean age 60.3 years, range 23–83) and in a group of 30 healthy volunteers (13 men, 17 women, mean age 54.5 years, range 20–73). The healthy subjects displayed no signs or symptoms of central or peripheral nerve system involvement, had no risk factors for peripheral nerve dysfunction and showed normal thermal thresholds in all the introductory tests performed. The reference values for the warm and cold perception thresholds were obtained from *Yarnitsky and Sprecher* (*12*). These authors employed the same apparatus with thermode size, baseline temperature, and rate of stimulus rise similar to the present study. All the neuropathic patients suffered from distal symmetrical subacute or chronic clinical symptoms of paresthesias and painful dysesthesias in the lower extremities, displayed a significant reduction of the number of intraepidermal PGP 9.5 immunoreactive small sensory nerve fibres in skin biopsy samples from the lateral aspect of the calf compared to the reference data published by *McArthur* (*13*), and showed abnormal thermal thresholds assessed by the first TTT examination.

Thermal thresholds were established using a Nicolet Viking IV electrodiagnostic unit, Thermal Sensory Analyser software (Medoc TSA 2001), and a rectangular constant thermal probe with a surface area of 5 x 2.5 cm. The starting (adaptation) temperature was 32 °C. In order to prevent thermal injury, the high temperature limit was set at 50 °C and the low one at 0 °C.

In all the subjects tested, thermal thresholds were examined at two locations: in the thenar of the left hand (TH) and in the dorsum of the right foot (DF).

At both locations, we used 3 different test algorithms: a random and a non-random variant of the method of limits (MLI), and one method of levels (MLE). We used the same settings of MLE and the non-random variant of the MLI, as previously described by other authors (*10*).

In the random variant of the MLI method, 5 cold and 5 warm stimuli alternated in random order and the subject was asked to indicate the onset of sensation and to decide which thermal modality was perceived to disclose any disturbance of thermal modality discrimination.

In each of the algorithms tested, both cold (CP) and warm (WP) perception thresholds were assessed. All the tests were performed in exactly the same manner and by the same examiner (EM) in a quiet room with no distractions.

Statistical methods

As a quantitative measure of reproducibility, the standard deviation of the differences between pairs of repeated measurements of each test (SD_{dif}) was calculated as $\sqrt{\Sigma d_{iff}^2/n}$, where n represents the number of all measurements (i.e. two times the

number of patients examined by the particular test). The coefficient of repeatability (CR) was expressed as 2 multiple of SD_{dif} (*14*). A variance ratio test (*15*) was used to disclose and quantify differences in the reproducibility of thermal threshold assessment between the different testing algorithms and groups of patients. The relationship between the threshold value and the differences between the repeated measurements was tested by means of Pearson's correlation test. A value of $p < 0.05$ was taken as the universal indicative limit for statistical significance.

RESULTS

The greater part of the neuropathic patients (70 %) exhibited disturbed perception of cold stimuli; they felt cold stimuli as warm or hot (paradoxical sensation), while warm stimuli were always perceived correctly as being warm. This type of perception was always presented in both of the repeated measurements and was never observed in the group of healthy volunteers. Some SFN patients were repeatedly and completely unable to perceive cold (12 %) and/or warm (9 %) stimuli during RTI tests in both examinations (they reached the maximum/minimum temperature of $50^0/0^0$C without reporting any thermal perception at all). The data from patients with anaesthesia for cold and/or warm thermal stimuli were excluded from further computation.

We found a significant positive correlation between the thermal threshold values and the differences between repeated measurements in most of the tests, particularly in healthy subjects.

The coefficients of repeatability are summarised in *Table 1*. The comparison between tested groups showed better reproducibility of all tests in TH and in CP tests in DF in a group of healthy volunteers in comparison with neuropathic patients (<0.001). The differences in reproducibility of WP tests between healthy and neuropathic subjects in DF were not significant (p= 0.27–0.38).

In both groups, all the tests showed better reproducibility in the TH than in the DF (p= 0.005– <0.001).

The reproducibility of cold thresholds in both groups was higher in the method of levels in comparison with that of limits. In WP tests the differences between various algorithms were not significant. No differences were found between random and non-random variants of MLI.

As far as the influence of tested thermal modality on the reproducibility of the threshold values is concerned, cold threshold assessment in the DF showed significantly lower reproducibility in comparison with warm threshold assessment in neuropathic patients ($p < 0.001$). Surprisingly, in the group of healthy volunteers the differences were inverse: cold threshold values in this location (DF) were more reproducible ($p < 0.001$).

In the subgroup of patients who displayed the "paradoxical sensation" in DF, the reproducibility was not significantly different from those with normal discrimination between thermal modalities.

Table 1

Coefficients of repeatability (CR) expressed as 2 multiple of $SD_{dif.}$ This parameter represents 95 % confidence that the second measurement will lie in the interval defined as the first measurement ± CR and can be used as the upper normal limit for intraindividual change during repeated tests.

Algorithm and tested location	2 $SD_{dif.}$ (°C)		
	Healthy volunteers	Neuropathic group	p values
TH: MLI NR CP	1.06	2.18	<0.001
MLI NR WP	0.76	1.38	<0.001
MLI R CP	0.71	1.40	<0.001
MLI R WP	0.72	1.56	<0.001
MLE CP	0.48	1.22	<0.001
MLE WP	0.54	1.24	<0.001
Mean of all tests	0.72	1.50	
DF: MLI NR CP	1.16	5.74	<0.001
MLI NR WP	3.00	2.84	n.s.
MLI R CP	1.66	5.04	<0.001
MLI R WP	3.98	2.66	n.s.
MLE CP	0.90	3.12	<0.001
MLE WP	2.38	2.62	n.s.
Mean of all tests	2.18	3.68	

TH – thenar of the hand; DF – dorsum of the foot; CP – cold perception; WP – warm perception; R – random variant of the test; NR – non-random variant of the test; MLI – method of limits; MLE – method of levels; n.s. – non-significant; SDdif. – standard deviation of the differences – expressed in °C

DISCUSSION

This is the first study to show lower reproducibility of thermal threshold assessment in a group of small-fibre neuropathy patients compared with normal subjects and using different algorithms.

In general, there is little published data available to compare the reproducibility of different groups of subjects and different methods. Moreover, these studies have shown no general agreement on the issue of difference in the reproducibility of thermal thresholds between healthy individuals and patients with abnormal threshold values. Several authors (*3*) have reported similar reproducibility of thermal thresholds in healthy individuals and patients with diabetes mellitus, while others (*8*) found worse reproducibility of the method in diabetic patients. The discrepancy between the results in previous studies could be caused by different inclusion criteria in various study groups, especially by the different degree of thermal threshold abnormality. In our group, the involvement of small fibres was documented by skin biopsy in addition to abnormal thermal thresholds detected by TTT. Another cause of this discrepancy could be the lack of consensus as to how repeatability should be defined (*3, 11*). We used the coefficient of repeatability (*14*), also known as "the repeatability factor" by others (*1, 11,12*). It represents 95 % confidence that the results of two examinations made on the same subject under the same conditions will differ less than CR and therefore can be used as a limit of the incidental (i.e. non-significant) intraindividual change of the thermal threshold on a longitudinal follow-up.

The CRs in our material varied substantially among the different tests, body regions, thermal modalities, and the two groups tested. In general, reproducibility was decreased by all factors increasing the value of threshold temperature. The threshold values were less reproducible in patients with abnormal thresholds in comparison with healthy individuals and in the foot in comparison with the hands.

Other possible causes of discrepancies between the various studies may lie in differences between the algorithms employed. *Yarnitski and Sprecher* (*12*) reported a lower reproducibility of the method of limits in comparison with the MLE. *Kemler* (*10*) confirmed this difference in reproducibility in the hands, but not in the feet. Others, however, reported no such difference (*2, 9*). In our study, the coefficients of repeatability of cold perception thresholds were significantly better for MLE than for MLI. The difference between the tested algorithms probably results from the influence of reaction time upon the threshold value.

The modality tested also seems to have some influence on the reproducibility of threshold values. In our group of polyneuropathy patients, we found a significantly lower reproducibility of cold thermal threshold values in comparison with warm threshold values. These results are similar to those in diabetic patients reported by *Hilz* (*8*) and *Valensi* (*9*) and might be explained by the disturbance of cold modality discrimination in a major part of our SFN patients. Many of these patients felt cold stimuli as warm or hot (paradoxical sensation), while warm stimuli were perceived

correctly as being warm. Similar findings of disturbed cold modality discrimination have previously been reported by other authors (*4, 16*). In contrast with the SFN results, the reproducibility of cold thresholds in our group of healthy volunteers was even better than of the warm sensation thresholds. Such a difference might be explained by the above-mentioned positive correlation between the absolute threshold value and the difference between repeated measurements. In healthy subjects, cold threshold values were significantly lower in comparison with warm sensation values. Similarly, no signs of worse reproducibility of cold thresholds in healthy subjects were found by *Doeland* (*6*) and *Hilz* (*8*).

In conclusion, the long-term follow-up of thermal threshold changes of small-fibre polyneuropathy patients should be interpreted carefully. If TTT is intended to be used as a method for longitudinal assessment of small nerve fibre function, the thermal threshold value of the patient, localisation of the thermode, and the algorithm tested should be taken into consideration. The limits for the significant intraindividual change from healthy individuals cannot be recommended for use in patients with polyneuropathy, because of significant differences in the reproducibility of threshold values between healthy subjects and patients with abnormal thermal thresholds.

From the repeatability point of view, the method of levels and warm sensation testing are to be preferred

A c k n o w l e d g e m e n t

The study was supported by the Research Plan of the Czech Ministry of Education MSM0021622404.

Moravcová E., Bednařík J., Svobodník A., Dušek L.

REPRODUKOVATELNOST HODNOCENÍ TERMICKÉHO PRAHU U NEMOCNÝCH S NEUROPATIÍ TENKÝCH VLÁKEN

S o u h r n

Cílem bylo zhodnotit reprodukovatelnost stanovení termického prahu u nemocných s neuropatií tenkých vláken.

Metodika: Termický práh pro chlad a teplo byl opakovaně stanoven během 1 týdne ve skupině 58 nemocných s neuropatií tenkých vláken a u 30 zdravých dobrovolníků. Práh byl hodnocen na ruce a noze s pomocí 3 různých vyšetřovacích algoritmů.

Tzv. koeficient reprodukovatelnosti ("repeatability factor" vyjádřený jako dvojnásobek standardní odchylky rozdílů SD_{dif} vypočítané podle vzorce $SD_{dif}=\sqrt{\sum rozdíly^2/n}$, kde n představuje počet všech měření) kolísal mezi 0,72° a 1,5 °C na ruce a mezi 2,2 °C a 3,7 °C na noze u zdravých dobrovolníků a nemocných s neuropatií tenkých vláken. Reprodukovatelnost všech testů na ruce a testů prahu pro chlad na noze byla vyšší u zdravých dobrovolníků ve srovnání s nemocnými s neuropatií tenkých vláken. Hodnoty termického prahu jak u nemocných s neuropatií tenkých vláken, tak u zdravých dobrovolníků vykazovaly vyšší reprodukovatelnost na ruce ve srovnání s nohou. Hodnoty prahu pro chlad ve skupině nemocných s neuropatií tenkých vláken na noze se vyznačovaly nižší reprodukovatelností ve srovnání s hodnotami prahu pro teplo, zatímco ve skupině zdravých dobrovolníků byla

nalezena opačná závislost. Hodnoty prahů získaných metodou Úrovně měly vyšší reprodukovatelnost ve srovnání s hodnotami získanými metodou Limity.

Při použití stanovení termického prahu pro longitudinální sledování funkce somatických tenkých vláken u nemocných s neuropatií tenkých vláken a poruchou termické percepce je třeba použít rozdílných limitů pro náhodné intraindividuální změny hodnot termického prahu než u zdravých jedinců. Testovaná modalita, testovací algoritmus a testovaná kožní oblast mají rovněž významný vliv na reprodukovatelnost hodnot termického prahu.

REFERENCES

1. *Yarnitsky D.* Quantitative sensory testing. Muscle Nerve 1997; 20(2): 198–204.
2. *Claus D, Hilz MJ, Neundorfer B.* Thermal discrimination thresholds: a comparison of different methods. Acta Neurol Scand 1990; 81(6): 533–40.
3. *De Neeling JN, Beks PJ, Bertelsmann FW, Heine RJ, Bouter LM.* Sensory thresholds in older adults: reproducibility and reference values. Muscle Nerve 1994; 17(4): 454–461.
4. *Dyck PJ, Zimmerman I, Gillen DA, Johnson D, Karnes JL, O'Brien PC.* Cool, warm, and heat-pain detection thresholds: testing methods and inferences about anatomic distribution of receptors. Neurology 1993; 43(8): 1500–1508.
5. *Navarro X, Kennedy WR.* Evaluation of thermal and pain sensitivity in type I diabetic patients. J Neurol Neurosurg Psychiatry 1991; 54(1): 60–64.
6. *Doeland HJ, Nauta JJ, van Zandbergen JB, et al.* The relationship of cold and warmth cutaneous sensation to age and gender. Muscle Nerve 1989; 12(9): 712–715.
7. *Gelber DA, Pfeifer MA, Broadstone V, et al.* Components of variance for vibratory and thermal threshold testing in normal and diabetic subjects. J Diabetes Complications 1995; 9(3): 170–176.
8. *Hilz MJ, Claus D, Neundorfer B.* Early diagnosis of diabetic small fiber neuropathy by disturbed cold perception. J Diabet Complications 1988; 2(1): 38–43.
9. *Valensi P, Attali JR, Gagant S.* Reproducibility of parameters for assessment of diabetic neuropathy. The French Group for Research and Study of Diabetic Neuropathy. Diabet Med 1993; 10(10): 933–939.
10. *Kemler MA, Reulen JPH, van Kleef M, Barendse GAM, van den Wildenberg FAJM, Spaans F.* Thermal thresholds in complex regional pain syndrome type I: sensitivity and repeatability of the methods of limits and levels. Clin Neurophysiol 2000; 111: 1561–1568.
11. *Shy ME, Frohman EM, So YT, et al.* Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Quantitative sensory testing: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2003; 60(6): 898–904.
12. *Yarnitsky D, Sprecher E.* Thermal testing: normative data and repeatability for various test algorithms. J Neurol Sci 1994; 125(1): 39–45.
13. *McArthur JC, Stocks EA, Hauer P, Cornblath DR, Griffin JW.* Epidermal nerve fiber density: normative reference range and diagnostic efficiency. Arch Neurol 1998; 55(12): 1513–1520.
14. *Bland JM, Altman DG.* 1986. Statistical methods for assessing agreement between methods of clinical measurement. Lancet 1986; i: 307–310.
15. *Zar JH.* Biostatistical methods, 2nd ed. New York: Prentice Hall, 1982: p.125.
16. *Yosipovitch G, Yarnitsky D, Mermelstein V, et al.* Paradoxical heat sensation in uremic polyneuropathy. Muscle Nerve 1995; 18(7): 768–771.