

Validation of a Brazilian quantitative sensory testing (QST) device for the diagnosis of small fiber neuropathies

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ABSTRACT

Quantitative sensory testing (QST) is defined as the determination of thresholds for sensory perception under controlled stimulus. Our aim was to validate a new QST device for Brazilian sample. In 20 healthy adults, thermoalgesic thresholds were assessed using a QST prototype (Heat Pain Stimulator-1.1.10; Brazil). A 30 × 30 mm² thermode with a 1°C/s stimulus change rate were applied. Thresholds of three consecutive stimuli were averaged in two different sessions separated by at least two weeks. Additionally long thermal heat pain stimulus was performed. To evaluate the consistency of our method we also analyzed 11 patients with small fiber neuropathy. Results showed good reproducibility of thermal perception thresholds in normal individuals and plausible abnormal thresholds in patients. We conclude that our QST device is reliable when analyzing the nociceptive pathway in controls and patients.

Key words: quantitative sensory testing, validation, nociceptive pathway, psychophysics, heat pain stimulation.

Validação de um aparelho brasileiro de teste de quantificação sensitiva brasileiro para o diagnóstico de neuropatia de fibras finas

RESUMO

Teste de quantificação sensitiva (TQS) significa determinação de limiares de percepção sensitiva frente a um estímulo de intensidade controlada. Nosso objetivo foi validar um novo equipamento de TQS adaptado à população brasileira. Em 20 adultos saudáveis, limiares termoalgésicos foram avaliados, utilizando um aparelho protótipo do TQS (Heat Pain Stimulator-1.1.10; Brazil). Foi utilizado um termodo de 30 × 30 mm², com estímulo térmico de 1°C/s. A média dos limiares de três estímulos consecutivos foi obtida em duas sessões diferentes, separadas por pelo menos 2 semanas. Adicionalmente, foram aplicados estímulos térmicos dolorosos de longa duração. Para avaliar a consistência do nosso método, foram também analisados 11 pacientes com neuropatia de fibras finas. Os resultados mostraram boa reprodutibilidade dos limiares de percepção nos indivíduos saudáveis, assim como limiares anormais nos pacientes. Em conclusão, nosso aparelho de TQS apresentou boa confiabilidade ao analisar a via nociceptiva de controles e pacientes. **Palavras-Chave:** teste de quantificação sensitiva, validação, via nociceptiva, estímulo termoalgésico.

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Quantitative sensory testing (QST) is a widely used psychophysical method for quantification of sensory function^{1,2}. Although this method gives valid informa-

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tion on large fiber status, the term “QST” is normally used for small fiber and nociceptive pathway assessment, using controlled thermal, instead of tactile or vibratory stimuli³⁻⁶. This method is important for the diagnosis of neuropathies for two main reasons. First, because small fiber dysfunction is usually the first alteration in axonal neuropathies (i.e., diabetic) the QST could aid in its early diagnosis⁷. Second, contrary to QST, conventional nerve conduction studies are unable to assess small fiber function¹.

Differently than nerve conduction studies, QSTs are psychophysical in nature, requiring cooperation from the patient². While the sensory stimulus is controlled by the examiner during QST, the response represents the subjective perception of thermoalgesic stimulus. If abnormal, the QST result may signalize dysfunction anywhere along the sensory pathway between thermal receptors, small fibers, spinothalamic tract and other cerebral areas i.e. pain matrix⁸.

But how is perception measured? By means of controlled thermal stimuli, the patient is asked to press a button when he (she) feels different thermal perceptions from a thermode device in contact with the skin. Warm perception thresholds are used as a parameter reflecting the function of unmyelinated C-fibers, whereas heat pain and cold perception thresholds indicate A δ -fiber function; and to a lesser extent also the function of subgroups of C-fibers^{9,10}. However, in clinical routine, because cold thresholds are more variable, warm and heat pain thresholds are measured preferentially². Figure 1 shows the most common QST abnormalities in different clinical conditions⁸.

In the last few years QST has been one of the main methods used in human experimental pain models and in the early diagnosis of neuropathies^{6,11}. However, although considered an important tool in Neurology, QST devices are not easily available in most neurophysiologic laboratories worldwide. One of the reasons for such a

lack of availability is the high cost and the complexity of the grading sensory system. In Brazil, few centers have been developing QST devices^{12,13}, but no validation studies have been reported so far. Our aim is to show our experience in the development of a new computer-controlled thermal stimulation device, demonstrate its reliability in repetitive sessions within controls and patients and propose standardized QST verbal instructions for Brazilian patients.

METHOD

Subjects

We selected 20 healthy volunteers (10 men) aged from 22 to 44. We excluded subjects with peripheral nervous system diseases or using medication that could affect the sensory perception, such as psychotropic and analgesic medications. All subjects assigned the informed consent that was approved by the ethics committee of the Hospital de Clínicas de Porto Alegre, Brazil.

Patients

We selected 11 age- and sex-matched patients with painful neuropathies from the Neuromuscular Ambulatory from our institution, six of them with diabetes mellitus, four with leprosy and two with human immunodeficiency virus. All of them complaining of typical neuropathic pain over distal extremities.

Equipment

The system for heating/cooling of the thermal stimulator was based on Peltier principle. This module is a thermoelectric element which generates a temperature difference between the two sides of the component, coupled to an aluminum polished surface (Fig 2A) that gets in contact with the patient's skin (Fig 2B). The aluminum plate temperature is monitored by a temperature sensor,

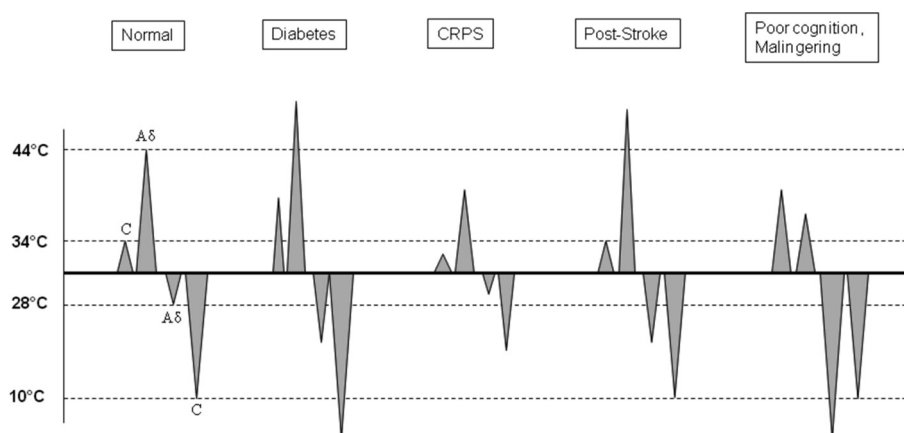


Fig 1. The most common quantitative sensory testing abnormalities in different clinical conditions⁸.

which has a response time of tenths of a second. The analog temperature after conditioning was sampled with 100 Hz and recorded with a 10 bit resolution. This sign is displayed in real time on the computer screen and is used to control the module temperature. This control is performed by the microcontroller that generates a pulsed signal applied to the power stage, which provides the current levels for the Peltier module excitation. The temperature of the thermode rised in a constant rate or stabilized in a pre-defined temperature during the experiment. To ensure this constant rising of temperature, a digital controller was implemented through software developed in visual basic platform on personal a computer. The patient can stop the heat at any time if he/she feels discomfort. In this case, temperature and time interval are monitored. Apart from the button that is used to mark the temperature in which the subject feels warm and heat pain sensations, the system also provides a linear analog input to inform, by means of a manual lever (Fig 2C), the intensity of discomfort on a visual analogue scale ranging from 0 (no discomfort) to 10 (intolerable pain). The system has an additional safety device, that automatically turns off the module when temperature reaches 52°C in order to avoid skin damage. The temperature and pain analog scale curves were stored in files for later analysis. Figure 3 shows a scheme of QST set up.

Experimental procedure

The evaluation was performed in a quiet, semidark room, at a temperature between 23°C and 24°C. Subjects were always addressed by the same researcher (LCS), who systematically read the instructions and explained the standardized experimental procedure, using a previously published QST protocol orientation¹⁴ adapted to Brazilian portuguese language.

Thermoalgesic stimuli were delivered through a Peltier thermode of a surface of 30 × 30 mm² (Heat Pain Stimulator-1.1.10, Brazil). Baseline temperature was always set at 30°C and ramp rate was fixed at 1°C/s, to a maximum at 52°C. Subjects were seated on a comfortable chair with arms on the armrest, and had the Peltier's thermode attached with a velcro strip to the ventral aspect of their mid forearm Figure 2B. We changed slightly the exact site of the skin where the thermode was applied between three consecutive trials. Subjects had an available button to press to immediately stop the thermoalgesic stimuli, when necessary. For all tests, we used the same software to apply a controlled change in the thermode temperature. Subjects were requested to pay attention to the thermal sensation and avoid speaking, coughing or breathing deeply during the experiment. In order to confirm that the thermode was homogeneously heated we also perform termography (Eletrophysics,

PV320T) in some subjects. All signals were represented on a screen out of the subject's visual field, for on-line monitoring and off-line analysis.

We assessed warm and heat pain thresholds, as well as sensory perception during long 45°C thermal stimulation, in two different occasions with an at least two-week interval for each subject.

Warm and pain thresholds

Warm and pain thresholds were assessed with the method of limits². The thermode was placed on the non-dominant upper arm. After a warning signal, the temperature rose from an adaptation temperature of 30°C with a ramp rate of 1°C/s. The participant was asked to press as quickly as possible a button at the moment the stimulation became warm or painful. Three assessments were taken with an interstimulus interval of 40 seconds¹⁵ and thresholds were calculated by taking the average temperature of the three assessments.

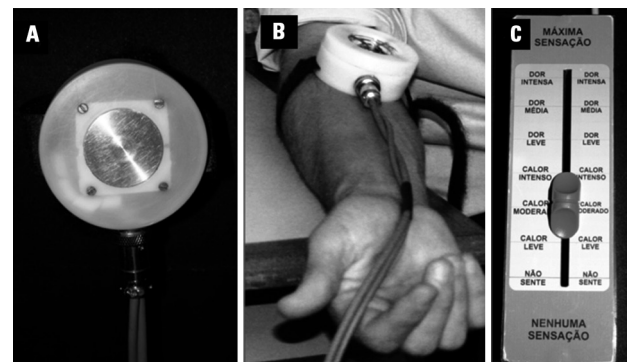


Fig 2. Quantitative sensory testing devices: [A] Thermode; [B] Position of the thermode in the arm; [C] Electronic visual analogue scale.

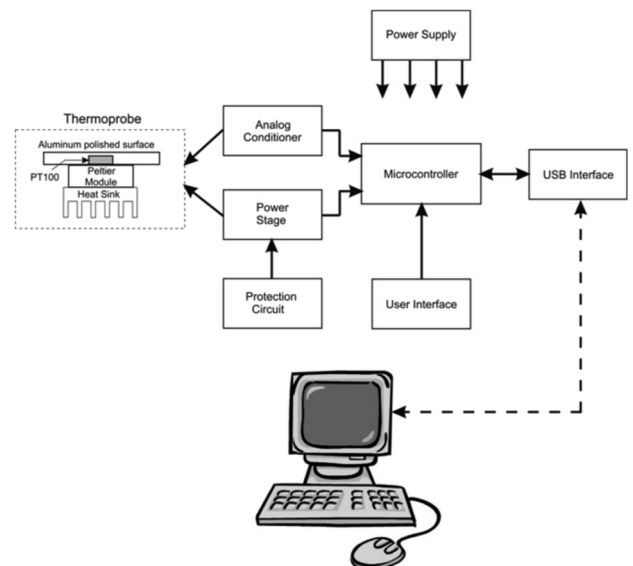


Fig 3. The quantitative sensory testing set up scheme.

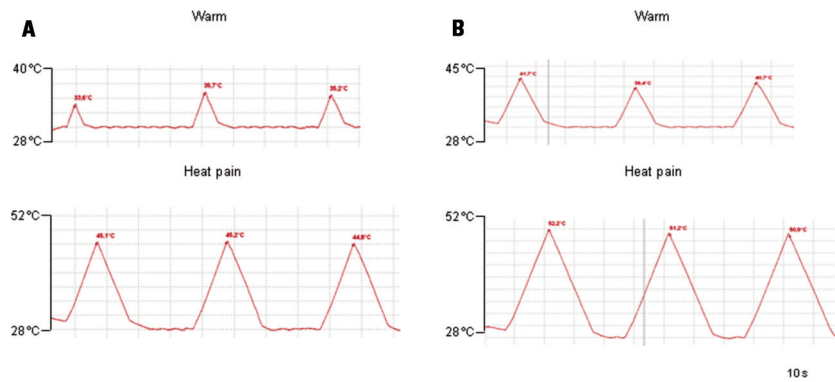


Fig 4. Thermal thresholds in normal subjects [A] and patients with small fiber disease [B]. Note higher thresholds for warm and pain sensation in a illustrative patient.

Long painful thermal stimulation

The thermode temperature was rapidly increased up to 45°C. Then, this temperature was maintained for 60 seconds. During this time, subjects marked their perception using an electronic visual analogue scale (VAS), with six different levels of perception:¹⁵ [1] no temperature perception; [2] light warm; [3] medium warm; [4] light pain; [5] medium pain and [6] high pain perception. We considered levels 2 and 4 as thresholds for warm and pain, respectively.

Statistical analyses

All statistical analyses were done using the Statistical Package for the Social Sciences (SPSS) for Windows version 16. Correlations between the indices of two separate measurements of warm threshold and heat pain thresholds were tested by Pearson coefficient. Also, the reproducibility of assessments was tested by intraclass coefficient. Student's t test was used for threshold comparisons between patients and controls. All analyses were performed with confidence interval of 95%.

RESULTS

Twenty healthy volunteers (10 females) participated in this study. Average age was 28±6.6 years. The correlation indices and intraclass coefficient average for warm and pain thresholds are presented in Table. No differences were found between thermal thresholds obtained with button versus electronic VAS (Student's t test; p>0.05 for all comparisons). When analyzing three patients with small fiber diseases and pain we observed elevated warm and heat thresholds in all of them. Figure 4 shows illustrative examples of normal (4A) and abnormal (4B) thresholds obtained from illustrative control subject and patient, respectively. Thermography recordings showed homogenous increment of skin temperature in a circumscribed area that exactly matched with the thermode dimensions (Fig 5). Although skin redness was observed in the vast majority of the subjects, no major skin injuries occurred in any of them. Subjective perception

during long painful stimulation followed a stereotyped pattern in controls. Most subjects moved the lever very rapidly; right after thermode had started to cool down. Differently, patients maintained the lever in pain sensation in the electronic VAS even after the thermode was cold. Figure 6 illustrates such differences showing another control subject (Fig 6A) and patient (Fig 6B) submitted to long painful stimulus.

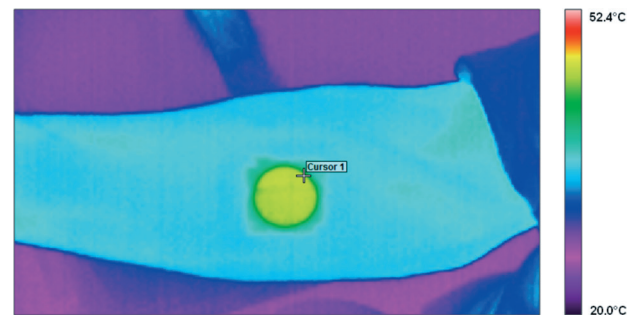


Fig 5. Thermography recording after heat pain stimulation. Note the size of the thermode imprinting in the skin and the actual achieved temperature.

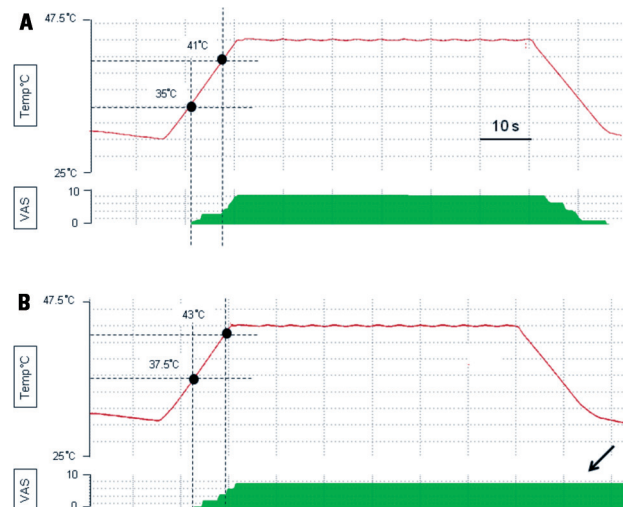


Fig 6. Long painful stimulation. Note the lower thermal thresholds of illustrative patient [B] in comparison with a control subject [A]. Also, note the persistency pain perception (black arrow) even after the stimulus has ceased.

Table. Mean and standard deviation values for thermoalgesic thresholds and correlation coefficients between quantitative sensory testing sessions.

Thresholds	Assessment		Pearson coefficient	Intraclass coefficient
	First	Second		
Warm (°C)	35.6±1.3	35.3±1.4	0.8*	0.88*
Heat Pain (°C)	44.5±2.5	43.3±2.9	0.91*	0.92*

*p<0.001.

Warm and heat pain thresholds were significantly higher in patients than in controls (39.4±1.4°C vs. 35.6±1.3°C, for warm and 49.9±3°C vs. 44.5±2.5°C, for pain perception; Student's t test; p<0.001 for all comparisons).

DISCUSSION

Our study has four main findings: [1] All thermal thresholds values were compatible with normal thermoalgesic transmission from warm and pain receptors to the brain; [2] All values were highly reproducible among time-separated measurements; [3] Thermal thresholds obtained with the button were the same obtained with electronic VAS and [4] As expected, abnormal thermal thresholds were observed in patients with small fiber dysfunction.

Several algorithms have been suggested to determine thermal perception thresholds^{3,9,16}. Two general schemes have emerged: the method of limits and the method of levels². In the method of limits, a subject is required to indicate as soon as an increasingly thermal stimulus is detected. Therefore this method is considered "time reaction inclusive". In the method of levels, stimuli of defined intensity levels are tested with the subject signaling whether a specific level is detected. In this case, thresholds are not dependent on reaction time and they are usually higher than the method of limits. Both tests are reliable, however the method of levels is time consuming (6 times longer than the method of limits) and no differences in sensitivity between the two methods were seen in diabetic patients¹⁷.

It is important to stress that QST does not measure pain itself. Actually QST measure sensory deficit that could be or not related to pain complaints. In a patient with chronic pain, lower thermal thresholds point to hyperalgesia, whereas elevated warm and heat pain thresholds point to a small fiber dysfunction which sometimes leads to neuropathic pain^{6,8,11,18}.

The thresholds for warm and heat pain stimuli obtained in this study are in agreement with previously published reports^{4,15,19,20}. In addition, psychophysical responses to long thermal stimulation were also similar to previous results²¹. An interesting finding was the greater variability of heat pain thresholds in comparison to warm

thresholds. This is in line with previous study²⁰ and may be explained by the fact that pain is greatly influenced by modulatory mechanisms²². The long thermal stimulation protocol also brought some interesting findings. Normal subjects almost always have their perception decreased after a few seconds of steady pain stimulation. This can be explained by the refractoriness of thermal receptors after prolonged excitation making the brain equivocally think that there is a transient reduction of sensation. Another curious finding was the maintenance of pain perception such as seen in an illustrative patient with small fiber disease. This can be assumed to be an after sensation phenomenon, a very typical finding in patients with neuropathic pain due to spinal central sensitization after peripheral lesions²³. These findings highlight the usefulness of an electronic VAS instead of a conventional and static button pressed when relevant perceptions are perceived. Besides, this strategy also serve not only as confirmation of the subject's ability to detect and perceive pain, but also as a method for monitoring the possibility that innocuous stimuli are painful in sporadic cases of allodynia phenomenon²⁰. Thus, incorporating simultaneous electronic VAS during thermal stimulation would make the QST more complete as a diagnostic procedure.

Apart from the accuracy of thermal thresholds we have also observed a very good reproducibility within subjects, which is in accordance with several authors²⁴⁻²⁷. In fact, the QST reproducibility in normal subjects is probably better than that of patients with neuropathy²⁸.

Our study has two main limitations. First we do not use thermodes with different ramp rates in different body sites. In the same way we only used a large thermode and this could not be sensitive enough to detect mild neuropathy because of spatial summation²⁹. However, the ramp rate and body location used in this study was mainly employed by others² and large thermode allows sensation to be more easily discriminated in normal skin³⁰ and provide more reproducible thresholds²⁶. Indeed, small thermodes should be used only at rounded body surfaces⁵. Second, we do not perform electrophysiological studies in order to confirm the absence of subclinical small fiber disease i.e., laser or contact heat-evoked potentials. However none of our subjects complained of any sensory disturbances neither have some risk factor for small fiber neuropathy.

Despite the limitations of our study, our QST device showed good accuracy and reproducibility in both controls and patients. Using QST, sensory deficits may be quantified and the data can be used in parametric statistical analysis. Therefore, this tool can reliably be used for research and clinical purposes adapted to Brazilian Portuguese language. Further studies are needed using different body regions and thermode sizes.

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