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Test Order of Quantitative Sensory Testing Facilitates Mechanical Hyperalgesia in Healthy Volunteers

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Abstract: **Quantitative sensory testing (QST) has become a widely used method to evaluate different submodalities of the somatic sensory system (predominantly) in patients with neuropathic pain. QST consists of 7 tests measuring 13 parameters in order to assess and quantify the perception of temperature, touch, pain, pressure, and vibration. The German Research Network on Neuropathic Pain implemented a standardized QST protocol including a defined testing order of the measurements. Accordingly, subjects tested with QST undergo thermal before mechanical testing. In the present study, we investigated the effect of testing order on the results of QST. Twenty healthy subjects were tested twice, 1 week apart with 2 different QST testing orders: the standardized testing order according to the German Research Network on Neuropathic Pain and a modified testing order in which mechanical stimuli were applied before thermal stimuli. For the test protocol that began with thermal testing, subjects exhibited signs of an increased mechanical perception: The mechanical pain sensitivity was significantly increased ($P = .001$, Wilcoxon test) for each pinprick stimulator and the mechanical pain threshold was lowered by a factor of 2 when compared with the modified testing order in which mechanical parameters were tested at the beginning of the session without prior thermal stimulation. Thermal parameters were the same for both test-order paradigms. These data indicate that preceding mild thermal stimulation might lead to a sensitization to mechanical stimuli and thus to mechanical hyperalgesia. Alternative habituation mechanisms in the modified testing order resulting from repeated pinprick stimulation at the beginning should also be debated. QST is a helpful diagnostic tool but interpretation should be done with consideration of interaction between test parameters. Reference data are only valid in the testing order from which they are obtained.**

Perspective: ***Present data showed that mechanical hyperalgesia followed thermal testing. This article demonstrates that the test order of quantitative sensory testing is relevant in interpreting the results obtained. Reference values are suitable in the test order from which they are obtained.***

Key words: *QST, mechanical hyperalgesia, test order, thermal stimuli.*

Quantitative sensory testing (QST) has been developed to evaluate different submodalities of somatic sensory functions. The application of calibrated mechanical, thermal, vibratory, and pressure stimuli activates nerve fibers of different size and allows the determination of both detection and pain thresholds. Combinations of sensory tests make it possible to detect and differentiate the sensory function of A-beta-, A-delta-, and C-fibers in patients with neurological symptoms, in particular in patients with neuropathic pain.[16,24,28]

QST represents an appropriate method to measure quantitatively sensory loss (hypaesthesia) as well as sensory gain (hyperalgesia, allodynia), both of which are characteristic for neuropathic pain. Thermal QST provides a diagnostic sensitivity for small-fiber neuropathy from 67

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to 100%.[15,34] The German Research Network on Neuropathic Pain (DFNS) implemented a standardized QST protocol[28] that improved the reproducibility and reduced the inter- and intra-individual variability.[9]

According to DFNS, the QST battery comprises 7 validated tests measuring 13 parameters that give information about the perception of temperature, touch, pain, pressure, and vibration.[28] Each test is administered in a standardized order. First, thermal stimuli are applied, followed by mechanical stimuli including stimulus-response tests (mechanical pain sensitivity for pinprick stimuli and dynamic mechanical allodynia for stroking light touch). Heat stimulation is known to increase or decrease subsequent responses to heat depending on intensity, duration, and test interval[2,12,30] and may also sensitize subsequent responses to mechanical stimuli.[4]

Therefore, the aim of this study was to establish the influence of test order on quantitative results of standardized QST testing according to DFNS in healthy subjects.

Methods

Study Design

This study was initiated as a prospective study to investigate the effect of test order on QST results. Twenty healthy volunteers were randomly divided into 2 groups. For both groups, QST was performed twice with a time interval of 1 week. One group first underwent QST in DFNS testing order followed by a second QST session using a modified testing order. The other group first underwent QST in modified order followed by the testing order according to DFNS. In both experimental sessions all stimuli were given unilaterally on a definite area localized on the dorsum of the hand; mechanical and thermal testing was performed at the same site which was in accordance with the DFNS protocol. In each group, subjects were randomly assigned to be tested on either the right or left hand.

Subjects

Twenty healthy human subjects were included in the study (11 female, 9 male; mean age ± SEM: 27.5 ± .9 years). All subjects participated voluntarily in the study after giving written informed consent. The study was carried out according to the principles of research in humans stipulated in the Declaration of Helsinki (revised form 2008) and the experimental protocol had prior ethical approval from the local Ethics Committee. Subjects were excluded if they had been diagnosed with or suspected to potentially have any form of neurological disease including different forms of neuropathy, systemic disease, chronic pain, cutaneous lesions in the tested area, or chronic substance abuse as well as an intake of pain medication in the 24-hour period prior to the investigation.

Quantitative Sensory Testing (QST)

DFNS developed a comprehensive QST protocol to improve the diagnostic value of QST and provide a broad basis of reproducible results.[28] Apart from the modification of the test order for 1 of the 2 experimental sessions, QST was performed in accordance to the DFNS protocol. Subjects were instructed in a standardized manner and were tested under identical conditions in a comfortable position in a quiet room with the ambient temperature controlled at 21 to 23°C. Subjects were not permitted access to the QST computer screen nor were they given visual or auditory cues to indicate the start of individual stimuli. During both QST testing sessions, the skin of the dorsum of the hand (sensory region of the radial and ulnar nerve) of the same body side was tested. One experimental session lasted about 30 minutes. All tests were carried out by EG who received intensive training from an experienced instructor (PML) to conduct QST according to the DFNS protocol.

Half of the subjects first underwent QST in DFNS testing order while the second half first underwent QST in a modified order. After an interval of 1 week, the testing order was reversed in the 2 groups. The different parameters of the standardized QST battery according to DFNS protocol began with the determination of thermal thresholds followed by mechanical thresholds and can be chronologically listed as follows:

- Cold and warm detection threshold (CDT, WDT);
- Number of paradoxical heat sensations (PHS) during thermal sensory limen procedure (TSL);
- Cold and heat pain threshold (CPT, HPT);
- Mechanical detection and pain threshold (MDT, MPT);
- Mechanical pain sensitivity (MPS) for pinprick stimuli;
- Dynamic mechanical allodynia (DMA) for stroking light touch;
- Wind-up ratio (WUR) during pain summation to repetitive pinprick stimuli;
- Vibration detection threshold (VDT);
- Pressure pain threshold (PPT).

To avoid the possible influence of skin deformation during mechanical stimulation, DFNS established a test order starting with measuring thermal thresholds.

In contrast to the common QST order according to DFNS, the modified QST battery started with the mechanical stimuli followed by the thermal stimuli. The parameters in the modified version were ordered as follows: WUR, MPS, DMA, PPT, VDT, MPT, MDT, CDT, WDT, PHS, TSL, CPT, HPT. More details on the QST protocol including reference data have already been published.[28] In brief, a short summary of the QST techniques used follows.

Thermal Testing

Tests for thermal sensations were performed by means of a Peltier-based computerized thermal stimulator (TSA II; Medoc Inc., Ramat Ishai, Israel) with a 3- × 3-cm contact probe.[8,38] The baseline temperature was 32°C. All thresholds were measured using ramped stimuli (1°C/s) until the subject pressed a stop button. Cut-off temperatures were 0°C and 50°C. At first, CDT and WDT