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Laboratory Studies

Thermal quantitative sensory testing: A study of 101 control subjects

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ABSTRACT

Quantitative sensory testing is useful for the diagnosis, confirmation and monitoring of small fibre neuropathies. Normative data have been reported but differences in methodology, lack of age-specific values and graphical presentation of data make much of these data difficult to apply in a clinical setting. We have collected normative age-specific thermal threshold data for use in a clinical setting and clarified other factors influencing reference values, including the individual machine or operator. Thermal threshold studies were performed on 101 healthy volunteers (21–70 years old) using one of two Medoc Thermal Sensory Analyser II machines (Medoc, Ramat Yishai, Israel) with a number of operators. A further study was performed on 10 healthy volunteers using both machines and one operator at least 3 weeks apart. Thermal threshold detection increases with age and is different for different body regions. There is no significant difference seen in results between machines of the same make and model; however, different operators may influence results. Normative data for thermal thresholds should be applied using only age- and region-specific values and all operators should be trained and strictly adhere to standard protocols. To our knowledge, this is the largest published collection of normal controls for thermal threshold testing presented with regression data which can easily be used in the clinical setting.

1. Introduction

Dysfunction of small unmyelinated nerve fibres is thought to be responsible for many painful peripheral neuropathies. These nerve fibres are unable to be evaluated by conventional nerve conduction studies making confirmation of diagnosis, monitoring of disease progression and objective evaluation of therapies for their disorders difficult.

Quantitative sensory testing (QST) is an automated psychophysical method used to indirectly test the function of these fibres. QST can be performed to assess various sensory modalities, including vibration, temperature, pinprick and pressure. Both stimulus detection and pain thresholds can be measured. QST is dependent upon the function of not only the peripheral nerve fibres but also the rest of the sensory pathway – including the dorsal root ganglia, spinal cord, thalamus and somatosensory cortex – as well as cognitive factors such as attention and reaction time.

Our study focused on thermal threshold QST, which assesses both unmyelinated C-fibres (warm detection and heat pain) and myelinated Aδ fibres (cold detection) [1]. Historically, thermal studies were designed to assess the warm-cold difference limen by the subject depressing a switch when a change in temperature was perceived. This is known as the Marstock method, named for the collaboration between the Marburg and Stockholm groups [2]. A modified Marstock method allows assessment of absolute thermal threshold by asking the subject to abort a gradually increasing thermal stimulus when it is perceived. The stimulus returns to a baseline of 32°C and the test is repeated a total of five times for warm and five times for cool sensation. The mean thermal threshold is recorded as the final value. The variability of the responses is also noted to ensure the test has been performed reliably. This is referred to as a method of limits. An alternate method, which presents the subject with a "yes/no" paradigm, known as the method of levels, may be more reliable but is more time consuming [3].

Our study aimed to collect normative age-specific data for thermal threshold detection using the modified Marstock method and to clarify whether other factors need to be taken into consideration

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when using normative data, such as the individual machine or operator.

2. Methods

One hundred and one normal volunteers (46 men, 55 women; aged 21–70 years [mean 43.4 years]) were studied. Data were collected by three operators using two different Medoc Thermal Sensory Analyser II machines (Medoc, Ramat Yishai, Israel) (operator G.L. used machine 1 and operators J.J. and M.L. used machine 2). The modified Marstock method of limits was used to record thermal thresholds for warm and cool detection at the thenar eminence of the right hand and over the dorsolateral aspect of the right foot.

As this initial study demonstrated an apparent difference between the two machines, an additional study was performed with a single operator (J.H.) studying a further 10 subjects (six males, four females; aged 17–62 years [mean 39.7 years]) using both machine 1 and machine 2 on each subject with at least 3 weeks between tests. Half of the subjects were examined first on machine 1 followed by machine 2, and the other half underwent testing in the opposite order. In contrast to previously described methodology, we did not employ a training stimulus prior to commencing the formal testing. This reduced total test time.

For all studies, a 3.0×3.0 cm thermode utilising the Peltier effect was used to provide thermal stimulation. A baseline adaptation temperature of 32°C was applied for 5 minutes to each site prior to commencing testing. The thermode changed temperature at 1°C per second, returned to baseline at 1°C per second following subject response and remained at baseline (32°C) for 4–6 seconds prior to delivering the next stimuli. The temperature range of the thermode was 0–50°C. Scripted verbal instructions were used to administer the test. Warm detection was measured five times at each site followed by cool detection measured five times at each site. The difference between the mean detection threshold and 32°C was recorded for warm and cool stimuli for each subject. The Medoc Thermal Sensory Analyser software produces a variance value (*varp*) for the five recordings from each modality. *Varp* levels greater than 5 in the hand and 10 in the foot were deemed to indicate unreliable testing from the spread of *varp* data, and any corresponding data were excluded from the final analysis.

Data were also excluded if the subject reported paradoxical sensations (i.e. reporting heat sensation during a cool stimulus), if the response was noted as an outlier within the age-group set, or if the subject reported significant pain at the level of thermal detection.

Statistical analysis was performed using Excel (Microsoft Corp., Redmond, WA, USA), SAS (SAS Institute Inc., Cary, NC, USA) and the Statistical Package for the Social Sciences software (SPSS, Chicago, IL, USA). To test for the effects of age, sex and operator/machine on detection thresholds, data were log-transformed and separate general linear models fitted in each combination of hand/foot and warm/cool threshold. The estimates from these models and the 95% confidence limits were back-transformed to calculate the effect of each variable as a factor. To predict upper limits of normal thresholds as a function of age, the raw detection thresholds were fitted to age only in linear regression models and the upper limit of the 99% prediction interval (corresponding to 2.5 standard deviations [SD]) calculated. In the 10 subjects who were tested by the same operator on the two different machines, paired differences were compared using *t*-tests to test for period and carry-over effects, and to estimate the effect of the different machines on the thresholds.

3. Results

One hundred and one subjects were recruited; their demographics are shown in Table 1. Two subjects were excluded from the entire analysis as they reported paradoxical heat sensations.

Table 1
Demographics of the healthy subjects enrolled in this study

Age, years	21–30	31–40	41–50	51–60	61–70	Total
Males	10	13	9	8	6	46
Females	12	9	10	15	9	55
Total	22	22	19	23	15	101

Two subjects with outlying results were excluded from the hand data. From the foot data, eight subjects were excluded from warm and three were excluded from cool analysis. This was due to pain at the thermal detection threshold (one warm, one cool); excessive variability of responses between five trials (seven warm; one cool); and outlying responses (one cool).

Mean thermal detection thresholds were calculated for age in years with the upper limit of normal taken as the 99% prediction limit (2.5 SD) (Fig. 1). This confirmed previously reported increased thermal detection thresholds with age [4]. Regression analyses produced equations (Table 2) demonstrating that the effect of age is most notable in the foot, where warm thermal thresholds increase by 1°C per decade of age. The effect is still significant but of smaller magnitude for other thermal threshold parameters. Upper limits of normal were tabulated by age for easy use in the clinical setting (Supp. Table 1).

The linear models fitted to log-transformed data showed there was strong evidence of a difference in thresholds in the hand depending on the machine used. This machine effect was not seen in the feet, which may be due to the larger thresholds being measured in this region. There was no evidence for an effect of sex on thresholds (Table 3). On machine 2, there was no evidence of a difference between the two operators (J.J. and M.L.) ($p \geqslant 0.4$ for all).

The additional study to clarify this finding of an apparent machine difference (10 subjects studied on both machines by a sole operator [J.H.]) showed no evidence of an effect on intra-individual results of inter-test interval or learning ($p \geqslant 0.36$ for all), though small effects may not have been detected due to the size of this sample. There was also no evidence of any difference between the machines (Table 4). This part of the study was powered to detect a difference in thermal threshold between machines of 1 SD. This suggests that the initially observed machine difference may have been related differences between an individual operator (G.L.) and the two operators (J.J., M.L.).

4. Discussion

Thermal threshold testing is a psychophysical method of assessing the function of the sensory pathways, including small nerve fibres, which are not assessed by traditional nerve conduction studies. The modified Marstock method is increasingly finding a role in the assessment and diagnosis of small fibre neuropathies including those seen in diabetes mellitus, renal failure and human immunodeficiency virus infection, as well as central sensory dysfunction (for example, post-stroke pain) and various pain syndromes (for example, angry backfiring C fibres syndrome, and cold hyperalgesia, cold hypoaesthesia, and cold skin syndrome) [5].

4.1. Normative data for QST

Normative data for thermal threshold testing have been reported previously, but differences in methodology, lack of age-specific values, and graphical rather than numerical presentation make much of these data difficult to apply to a modern clinical setting [1,2,4,6–10]. To our knowledge our study provides the largest single-centre cohort of normative thermal threshold detection data reported by age in years in a format that is easily applied to the clinical setting (Supp. Table 1). These data have been collected on