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Research paper

Method-of-limits; Cold and warm perception thresholds at proximal and distal body regions

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ABSTRACT

Objective: Thermal quantitative sensory testing with the 'Method-of-Limits' is an established rationale for detection of small nerve fiber dysfunction, but adequate reference values are crucial for such evaluations, regardless of the underlying cause. This study assessed reference data for cold- (CPT) and warm- (WPT) perception thresholds at both proximal and distal sites in eight body regions of the lower and upper extremities, all determined within the same test session for each subject.

Methods: Seventy-five healthy subjects (aged 16–72 years) were tested according to the method-of-limit for CPT and WPT at the dorsum of the foot, the medial and lateral lower leg, the ventral thigh, the thenar eminence, the radial and ulnar part of the lower arm, and the anterior deltoid part of the upper arm.

Results: Overall, thermal perception thresholds (TPT) varied with test location, but were higher in the lower than in the upper part of the body, also WPT were generally higher than CPT. TPT at the dorsum foot highly correlated with age, while inconsistent correlations were noted between TPT and age or height at other tested locations.

Conclusion: This study describes for the first time reference values at eight defined body regions, at both proximal and distal sites.

Significance: The report enables refined evaluations of general small nerve fiber function, as assessed by quantitative thermal sensory testing with the Method-of-Limits.

1. Introduction

Quantitative sensory testing (QST), of cold- (CPT) and warm- (WPT) perception thresholds is a well-established method for detection of small nerve fiber dysfunction, particularly in an early stage of debuting generalised and occasionally painful small fiber neuropathies (Abad et al., 2002; Heldestad and Nordh, 2007; Hendriksen et al., 1993; Hoitsma et al., 2003; Krämer et al., 2004; Løseth et al., 2008), in which patients develop symmetric and distal symptoms of peripheral nerve dysfunction (Hughes, 2002), yet showing normal findings in nerve conduction studies or needle-EMG examinations (Heldestad and Nordh, 2007; Løseth et al., 2008). Neurophysiological studies of C-receptor properties (Weider et al., 1999; Schmidt et al., 1995), have demonstrated that some C-fiber receptors may exhibit hyperactivity, indicating that the pain in patients with proposed 'painful small fiber neuropathy' not necessarily need to be caused by a generalised neuropathic loss of small fibers. Thus, there is a need for a comprehensive rationale for detailed descriptions of the functional state in the thin nerve fibers in diseases with suspected small fibre affection, with or without distal pain. Early assessment of small fibers neuropathy is also of value to prevent from secondary foot ulcerations (Cornblath, 2004) or other types of tissue damage in diabetic patients, and may even be critical in particular diseases like hereditary Amyloidotic transthyretin polyneuropathy, where an early detection of polyneuropathic changes may favour the outcome of symptomatic treatment by liver transplantation (Adams et al., 2000; Jonsén et al., 2001; Suhr et al., 2005), or new emerging pharmaceutical treatment (Berk et al., 2013; Coelho et al., 2012).

The implementation of thermal QST is hampered by that several testing algorithms are being used (Dyck et al., 1993; Fruhstorfer et al, 1976; Lin et al., 2005; Yarnitsky, 1997; Yarnitsky and Sprecher, 1994). For clinical use, the reaction-time inclusive 'Method-of-Limits' can be recommended, as it comprises a quick, reliable and easy-to-use rationale (Heldestad et al., 2010; Krøigård et al., 2015). Regardless of the method used, several factors influence the magnitude of the noted thresholds. Due to spatial summation (Kandel et al., 2012; Schmidt, 1978), the size

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of the stimulation probe is crucial (Dyck et al., 1993; Hilz et al., 1998, 1999), as well as differences in the number of receptors (Guergova and Dufour, 2011; Kandel et al., 2012; Schmidt, 1978) and in the density of nerve terminals between body areas (Chang et al, 2004). Also the velocity of temperature change during stimulation (Palmer et al., 2000; Pertovaara and Kojo, 1985), and the initial skin temperature is of importance (Hagander et al., 2000; Hilz et al., 1995), together with factors such as gender, age and the site of stimulation (Blankenburg et al., 2010; Defrin et al., 2006; Dyck et al., 1993; Hafner et al., 2015; Hagander et al., 2000; Hilz et al., 1999; Huang et al., 2010; Lin et al., 2005; Magerl et al., 2010; Meier et al., 2001; Yarnitsky, 1997; Yarnitsky and Sprecher, 1994).

To enable full evaluation of small fiber dysfunction, thermal QST should provide CPT and WPT reference data for both distal and proximal body regions. Although there are several reports on normative values for QST, both from single centre as well as from multi-centre studies, there is yet no comprehensive study describing full normative data for multiple body regions derived from the same group of healthy subjects. Previously reported reference data mostly assess distal sites in the lower and upper extremities (Blankenburg et al., 2010; González-Duarte et al., 2016; Hafner et al., 2015; Lin et al., 2005; Malmström et al., 2016; Magerl et al., 2010; Meier et al., 2001; Rolke et al., 2006; van den Bosch et al., 2017; Yarnitsky and Sprecher, 1994), although some of the studies also include the face (Blankenburg et al., 2010; Magerl et al., 2010; Rolke et al., 2006).

The purpose of the present study was to estimate cold and warm perception reference thresholds with the Method-of-Limits at different test sites both in the upper and lower extremities and in the same group of subjects. The aim was to define reference values for the cold and warm perception thresholds at distal and proximal parts of the extremities at eight different test sites, assessed from the same population of control subjects.

2. Methods

2.1. Subjects

Seventy-five subjectively healthy subjects initially volunteered for the study (37 men and 38 women (mean age 39 years, median 38, range 16–72 years), divided at 45 years of age into two groups (cf. Table 1 A and B for details). All had given their informed consent according to the World Medical Association's Declaration of Helsinki, and the Regional ethics committee of Northern Sweden approved the study. The immediate exclusion criteria were any sensory symptoms in the extremities, like diffuse numbness, dysesthesias and hyperesthesias, prickling, disturbances in cold- and/or warm perception, or any form of pain. Likewise, any signs, symptoms or diagnosis of diabetes, focal or general neuropathies, cervical spinal injuries excluded subjects from participation. At a further routine neurological status screening none of the initially recruited subjects showed any signs of reduced or asymmetric motor functions or muscular atrophies, nor did they show any signs of abnormalities in tactile or painful stimulus detection. However, during the actual thermal testing procedure a few subjects (n = 7) verbally reported symptoms of locally impaired warmth sense in the feet and/or at the medial or lateral aspects of the lower leg. These comments were taken as a indication of possible small fiber dysfunction, 'subclinical' lumbo-sacral nerve or spinal root affection, or of a localised alteration in central signal processing. These subjects' thermal data in the lower part of the body were therefore rejected in the final analysis. After these exclusions, the final study group consisted of sixty-eight subjects.

2.2. Thermal testing

QST was done with a 2.5 × 5.0 cm^2 computer controlled Peltier element (Thermotest®, Somedic AB, Hörby, Sweden). Totally nine test sessions were performed (including one training session), containing 10 individual cold respective warm stimulations with inter-stimulus intervals randomly varying between 3 and 5 s. During the testing the stimulation probe was manually held with firm contact to the subject's skin over the entire probe stimulating area. The subject was instructed to press an electrical switch as soon as the thermal stimuli were perceived; as soon as a sensation of the probe "becoming cooler" or "becoming warmer", for testing of cold and warm thresholds, respectively. The adapted skin start temperature was 32 °C (baseline temperature), and minimum and maximum temperatures were set to 10 °C and 50 °C, respectively, according to prevailing hospital safety regulations. The rate of change was set to 1 °C/sec during testing, and to 3 °C/s during return to baseline temperature.

2.3. Testing sites

Eight body sites were tested at randomly chosen side and order (cf. Fig. 1); the dorsum of the foot, the medial and the lateral aspect of the lower part of the leg, the ventral thigh, the thenar eminence, the radial and the ulnar part of the lower arm, and the deltoid anterior part of the upper arm.

2.4. Data conditioning and statistical analyses

Thermal data records were manually re-inspected after that each subject had ended the full testing procedure, to ensure data quality, and to remove responses reported by the subject as 'erroneous' or 'unintentional'. The CPT and WPT at each test site were defined as the mean value of the recorded consecutive individual thresholds in the recorded cold and warm sequences, respectively,

Table 1
Descriptive data of (A) all subjects pooled ($n = 75$); (B) subjects stratified by age (<45 years and ≥45 years) ($n = 75$).

A

Data	Range	Mean (Median)	Female/Male	Sides (Left/Right)
Age (years)	16.0–72.0	39.1 (38.1)		
Height (cm)	150–196	172.4 (172)		
Number			38/37	37/38

B

Age group	Years Range (Median)	Number Female/Men	Number Left/Right	Height (cm) Range (Median)
<45 years	16.0–45.0 (28.6)	22/24	24/22	154–190 (174)
≥45 years	45.0–72.0 (53.0)	16/13	14/15	150–196 (171)