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Contact heat evoked potentials: Reliable acquisition from lower extremities

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HIGHLIGHTS

- The increased baseline protocol improves acquisition of contact heat evoked potentials (CHEPs) from lower extremities.
- Reliability of CHEPs was better using increased baseline protocol for sacral and lumbar dermatomes.
- Improved CHEPs acquisition may strengthen its diagnostic utility in small fiber neuropathy.

ABSTRACT

Objective: To investigate test-retest reliability of contact heat evoked potentials (CHEPs) from lower extremities using two different stimulation protocols, i.e., normal and increased baseline temperature.
Methods: A total of 32 able-bodied subjects were included and a subset (N = 22) was retested. CHEPs were recorded from three different dermatomes of the lower extremity (i.e., L2, L5, and S2). Test-retest reliability of CHEPs acquisition after simulation in various lower limb dermatomes using different stimulation protocols was analyzed.
Results: The study revealed an improved acquisition of CHEPS employing the increased baseline protocol, particularly when stimulating more distal sites, i.e., dermatome L5 and S2. Based on repeatability coefficients, CHEP latency (N2 potential) emerged as the most robust CHEP parameter. Although CHEP amplitudes (N2P2 complex) and pain ratings were decreased in the retest, amplitudes still showed fair to excellent intraclass correlation coefficients using normal baseline or increased baseline temperature, respectively.
Conclusions: This is the first study to demonstrate that CHEPs acquisition from the lower extremities is improved by increasing the baseline temperature of the thermode.
Significance: This study highlights the usability of CHEPs as a viable diagnostic method to study small fiber integrity.

1. Introduction

Contact heat evoked potentials (CHEPs) reflect cortical responses of Aδ-nociceptors activated by noxious heat stimuli (Greffrath et al., 2007; Baumgartner et al., 2012). In addition to A-delta fibers, C-fibers are also known to be involved in the perception of contact heat. The reliable recording of C-fiber volleys is, however, extremely challenging (Magerl et al., 1999).

The late vertex component N2P2 has been used to assess the integrity of nociceptive pathways both in the peripheral and central nervous system (Atherton et al., 2007; Chao et al., 2008; Ulrich et al., 2013; Haefeli et al., 2014). In the clinical context, CHEPs emerged as a viable alternative to laser evoked potentials (Casanova-Molla et al., 2011) as they do not require complex safety

Abbreviations: CHEPs, contact heat evoked potentials; EP, evoked potential; NB, normal baseline; NRS, numeric rating scale; IB, increased baseline.

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measures (Casanova-Molla et al., 2011). The reliability, validity, and responsiveness of segmental cervical CHEPs were demonstrated in earlier studies (Kramer et al., 2012a,b; Ulrich et al., 2015; Jutzeler et al., 2016, 2017). In addition, CHEPS are well-suited to objectively assess length-dependent small fiber pathology, which often manifests first in lower extremities. Small fiber pathology is a hallmark of various disorders like diabetic neuropathy, thyroid dysfunction, sarcoidosis, vitamin B12 deficiency, HIV neuropathy, Fabry's disease, as well as drug-induced neuropathy (e.g., chemotherapeutic agents) (Tavee and Zhou, 2009). Large fiber function can be objectively and non-invasively assessed through nerve conduction studies and somatosensory evoked potentials (Botez and Herrmann, 2010). However, the assessment of sensory impairments due to small fiber dysfunction is restricted to either subjective verbal descriptors (Bouhassira et al., 2004) or pain questionnaires (Uceyler et al., 2014), quantitative sensory testing and skin biopsies (Devigili et al., 2008). Disclosing small fiber pathology is of diagnostic significance as etiological screenings or disease-modifying therapies should be initiated early on. Furthermore, small fiber pathology may precede larger-fiber impairments and can thus be suggestive of a concomitant subclinical involvement of large-diameter fibers (Herrmann et al., 2004; Sharma et al., 2007).

A number of studies have recorded CHEPs from the lower extremities (Atherton et al., 2007; Chao et al., 2010; Wong and Chung, 2011; Lagerburg et al., 2015). However, there is a lack of studies that systematically assess the reliability of CHEPs recorded from the lower extremities. One reason for this shortcoming constitutes the difficulty in the acquisition of nociceptive cortical potentials from the lower extremities (Lagerburg et al., 2015; Granovsky et al., 2016). Longer conduction distances to the brain are associated with higher latency jitter and a poorer signal-to-noise ratio (Magerl et al., 1999). One approach to enhance neuronal synchronization of the afferent volley is to shorten the stimulus duration by increasing the baseline temperature of CHEPs from 35 °C to 42 °C (Kramer et al., 2012a,b). Recent studies demonstrated that shortening the stimulus duration, i.e., increasing baseline temperature, substantially improves the acquisition of CHEPs from cervical dermatomes in ageing healthy controls and patients with spinal cord injury (Kramer et al., 2012a,b; Haefeli et al., 2014; Jutzeler et al., 2016).

To address these limitations, we recorded CHEPs from two lumbar (L2 and L5) and one sacral dermatome (S2) employing the conventional and increased baseline temperature approaches. The aim of the study was to assess the CHEP acquisition and reliability of both approaches. We tested the hypothesis that the increased baseline temperature approach will markedly improve the acquisition of lower extremity CHEPs resulting in good reliability.

2. Material and methods

2.1. Subjects

A total of 32 able-bodied subjects were recruited for this study. Inclusion criteria were (1) age between 20 and 60 years at the first examination and (2) native language either English or German. Exclusion criteria comprised pregnancy, intake of any psychoactive medication, and any neurological condition.

All subjects provided written informed consent prior to the assessment and all procedures described below were in accordance with the Declaration of Helsinki. The study has been approved by the local ethics board 'Kantonale Ethikkommission Zürich, KEK' (EK-04/2006, PB_2016-02051, clinicaltrial.gov number: NCT02138344).

2.2. Study design

In order to identify signs of peripheral neuropathy, all subjects were examined by neurologists. Additionally, nerve conduction studies and somatosensory evoked potentials were recorded to exclude significant large fiber pathology. Mechanoreception and nociception were semi-quantitatively assessed according to the grading system of the International Standards for Neurological Classification of Spinal Cord Injury (Kirshblum et al., 2011). Lastly, subjects were interviewed to assess their medical history.

The following three dermatomes of the right or left lower extremity were chosen for the CHEP recordings: L2 dermatome (inner side of the thigh), L5 dermatome (dorsum of the foot), and S2 dermatome (5 cm proximal to the popliteal fossa). The order of tested dermatomes and body side were randomized for each subject. CHEPs were recorded employing two different stimulation protocols: (1) the conventional *normal baseline protocol* followed by (2) the *increased baseline protocol*. The two protocols differ by their applied baseline temperature, i.e., 35 °C for the normal and 42 °C for the increased baseline protocol, while the peak temperature was set at 52 °C for both protocols (Kramer et al., 2012a,b; Kramer et al., 2013). The contact surface of the chosen dermatomes was sufficient allowing for a defined and evenly-distributed thermal stimulation of a cutaneous area.

Prior to the acquisition of CHEPs, a familiarization procedure was performed. This comprised of a normal baseline heat stimulus applied to the hand. To minimize movement and ocular artifacts, subjects were instructed to remain relaxed and reduce eye movement by fixating a point on the ceiling. Aiming at 15 artifact-free trials, 15–20 contact heat stimuli per protocol, i.e., normal and increase baseline, were applied with an inter-stimulus interval of 8–12 s. After each stimulus the thermode was slightly repositioned within the tested dermatome to avoid peripheral receptor fatigue and habituation (Greffrath et al., 2007). In addition, cued by an auditory signal provided 4 s after the heat stimulus, subjects were asked to rate the perceived intensity of each stimulus using a numeric rating scale ranging from 0 to 10 (NRS, 0 being no pain at all, 10 being worst pain imaginable).

For retest examination, 22 subjects were re-invited. The same protocol, including order of tested dermatome and body side, was used.

2.3. Acquisition of CHEPs

The CHEP measurement has been published elsewhere (Jutzeler et al., 2016). Briefly, the acquisition of CHEPs was performed with the PATHWAY Pain & Sensory Evaluation System (Medoc Ltd., Ramat Yishai, Israel) using a thermode of 27 mm diameter. Cortical potentials were recorded from the vertex position (Cz) using Ag/Cl electrodes referenced to the earlobes (A1-A2) according to the 10–20 system (Cruccu et al., 2008). The vertex position is considered as the most reliable position to record N2 and P2 potentials (Wydenkeller et al., 2008).

2.4. Data analysis and statistics

For both stimulation paradigms, a maximum number of 20 stimuli were applied. Trials contaminated with muscle or ocular artifacts were excluded online. In addition, two independent raters inspected the single trials offline for artifacts to have 15 artifact-free trials for further analyses. If there were more than 15 artifact-free signals, additional traces recorded at the end were discarded. The 15 artifact-free signals were averaged and the N2P2 waveform was visually detected.

All statistical analyses were performed using SPSS software (version 16) for Windows. R software for Windows (version