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Reliable estimation of nociceptive withdrawal reflex thresholds

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HIGHLIGHTS

- Withdrawal reflex thresholds can often not be estimated using sural nerve stimulation.
- A lower failure-rate may be obtained by eliciting the reflex at the arch of the foot.
- Electrical stimulation at the arch enables more reliable reflex threshold estimation.

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ABSTRACT

Background: Assessment of the nociceptive withdrawal reflex (NWR) is frequently applied to probe the excitability level of the spinal nociceptive circuitry. In humans, the NWR threshold (NWR-T) is often estimated by applying electrical stimulation over the sural nerve at the lateral malleolus. Such stimulation may be associated with substantial pain and discomfort rendering completion of the assessment infeasible.

New method: As an alternative to sural nerve stimulation, NWR-Ts were also estimated by electrical stimulation at the arch of the foot. Failure-rates and test–retest reliability of these two procedures were evaluated. A fully-automated interleaved up-down staircase procedure was used to estimate the NWR-T for both stimulation sites. NWRs were detected from EMG measured over the biceps femoris and tibialis anterior muscles, respectively. A total of three repeated measures were performed in two different sessions to evaluate the test–retest reliability of the two methods using Bland–Altman agreement analysis.

Results: The failure rate of NWR-T estimation based on electrical stimulation of the sural nerve (29%) was substantially higher than when the NWR was elicited by stimulation at the arch of the foot (5%).

Comparison with existing method: The analysis of test–retest reliability indicated that the two methods for NWR-T estimation were equally reliable for within-session comparisons, but stimulation at the arch of the foot enabled NWR-T estimation with superior between-session reliability

Conclusions: These results support a paradigm shift within NWR-T estimation favoring stimulation at the arch of the foot.

1. Introduction

The nociceptive withdrawal reflex (NWR) is a polysynaptic spinal reflex responsible for moving the limbs away from potentially harmful stimuli (Sandrini et al., 2005). There exists a close correlation between the NWR and experienced pain (Willer, 1977). Several independent investigations have provided evidence for NWR facilitation in patients with various pain conditions involving central mechanisms leading to increased neuronal responsiveness (Banic et al., 2004; Biurrun Manresa et al., 2013; Courtney et al., 2009; Desmeules et al., 2003; Lim et al., 2011, 2012; Neziri et al., 2010; Sandrini et al., 2006; Sterling et al., 2008). This indicates that the NWR threshold (NWR-T) constitute a valid measure of the excitability level of the spinal nociceptive system.

In humans, the NWR is generally elicited by electrical stimulation of the sural nerve at the lateral malleolus and measured

Abbreviations: CI, confidence intervals; CV, Conduction Velocity; CVA, Conduction Velocity Analysis; EMG, electromyography; LOA, Limits of agreement; NWR, nociceptive withdrawal reflex; NWR-T, nociceptive withdrawal reflex threshold.

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with surface EMG recorded over the ipsilateral brevis head of the biceps femoris muscle (Sandrini et al., 2005). However, the electrical stimulation applied directly over the sural nerve is often associated with substantial pain and discomfort. In both healthy volunteers and pain patients, a number of subjects find the painful stimulation intolerable and the assessment cannot be completed (Banic et al., 2004; Biurrun Manresa et al., 2014b; Sterling et al., 2008). In this way, the practical applicability of the NWR-T as a clinical measure of nociceptive excitability is reduced. Another concern related to this assessment methodology regards the reliability of the obtained measurements. Previous studies investigating the reliability of the NWR-T reported excellent within-session reliability but larger variability between sessions (Biurrun Manresa et al., 2011; Micalos et al., 2009) and it has been suggested that the variability may be caused to some extent by slight inconsistencies in electrode placement resulting in variation in neural activation by the electro-cutaneous stimulation over the sural nerve.

Methods for quantification of reflex receptive fields involve elicitation of the NWR by electrical stimulation applied to the skin under the sole of the foot and measurement of the NWR by surface electromyography (EMG) over the tibialis anterior muscle (Neziri et al., 2009). To most subjects, this procedure is more tolerable than sural nerve stimulation, increasing the likelihood of successful NWR-T estimation. Furthermore, it is hypothesized that stimulation of free nerve endings in the skin at the arch of the foot (the most sensitive area) is less prone to variations in electrode placement than transcutaneous stimulation applied directly over the sural nerve trunk. If so, this may result in a more reliable NWR-T assessment.

The present study investigates the practical applicability of the two methods for NWR-T estimation by evaluating the frequency with which each method fails to yield a successful NWR-T estimation and by examining the test–retest reliability of the two procedures.

2. Materials and methods

2.1. Subjects

Twenty one healthy volunteers (age: 18–35 years, 16 females) participated in the study. Written informed consent was obtained from all subjects prior to participation and the Declaration of Helsinki was respected. The study was approved by the local ethical committee (approval number VN—20130006).

2.2. Experimental procedure

Two individual estimations of the NWR-T were performed by applying electrical stimulation over the sural nerve and under the sole of the foot, respectively (Fig. 1). An automated staircase procedure was used for online NWR detection to allow for a completely objective evaluation. This experimental procedure was performed three times on each subject; two times in one double session (1 h pause between estimates, no replacement of electrodes) and one time in a single session. Sessions were 48 ± 1 h apart, and the order was randomized. The order of the two methods for NWR-T estimation was also randomized between subjects but kept constant between both intra- and inter-session reassessments for each individual subject.

2.2.1. Initial setup

Subjects were asked to refrain from caffeine, nicotine, alcohol and strenuous exercise for at least 4 h and from analgesic medication for 24 h prior to the experiment. During the experiment, the subject was placed in supine position with back support inclined 135 degrees relative to the horizontal level. A pillow was placed under the knees, resulting in a knee flexion of 45 degrees. Prior to actual data acquisition, the subject was thoroughly familiarized with electrical stimulation to reduce the effects of arousal or anxiety.

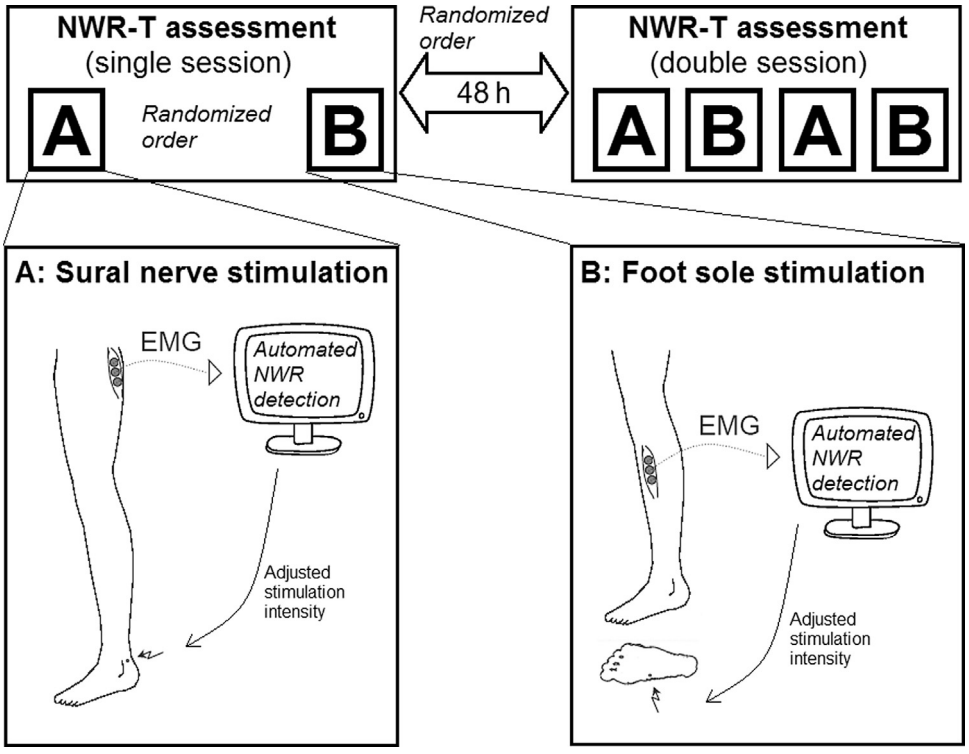

Fig. 1. Study design and overall methodology. The nociceptive withdrawal reflex threshold (NWR-T) was assessed using two different procedures (A and B) involving two different locations for electrical stimulation and EMG recording.