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A reappraisal of various methods for measuring motor nerve refractory period in humans

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Abstract

Objective: To compare various techniques of stimulation and methods of analysis to estimate absolute (ARP) and relative (RRP) refractory periods in motor nerve trunks of humans.

Methods: Double collision (DC) technique and two types of paired pulse (PP) technique, with test stimulation of supramaximal (PP^{supra}) or submaximal (PP_{sub}) intensity, were applied to 32 healthy subjects. The ulnar nerve was stimulated either at a single site (wrist) for the PP techniques or at two sites (wrist and elbow) for the DC technique, with various distal interstimuli intervals (ISIs). The elicited compound muscle action potentials (CMAPs) were recorded from the abductor digitorum minimi muscle. The DC technique provided estimates of minimal and maximal ARPs, whereas maximal RRP values were obtained with the PP techniques. Data were analyzed using three methods: a visual reading of the raw ISI–CMAP curves and two computer-aided analyses of the regression curve fitting the ISI–CMAP plots. Pain induced by each technique was assessed on a 0–10 visual analogue scale. A test-retest study was performed with the PP techniques in 12 subjects.

Results: RP estimates varied with both the stimulation technique and the analysis method. The DC technique was more painful than the PP techniques, but provided shorter and more accurate ARP values, whereas the PP_{sub} technique provided longer, but valid RRP values. Computer-aided methods of data analysis gave the lowest coefficients of test-retest variation.

Conclusions: Compared to the PP techniques, the DC technique allowed the evaluation of the whole distribution of ARP estimates, not distorted by muscle fiber RPs. For RRP estimation, the PP_{sub} technique can be preferred to the PP^{supra} technique. Finally, computer-aided methods are preferable to analyze ISI–CMAP curves.

Significance: The distribution of RP estimates can be easily and reliably assessed in whole motor nerve trunks of humans, providing valuable information to assess peripheral nerve excitability.

Keywords: Compound muscle action potential; Nerve excitability; Peripheral neuropathy; Refractory period; Voltage-gated sodium channel

1. Introduction

Following an action potential, peripheral nerve axons become unexcitable for the absolute refractory period (ARP), during which they cannot generate another action potential, whatever membrane solicitation. The axons pass then into the relative refractory period (RRP), during which a stronger than normal depolarizing stimulus is required to generate an action potential. The RRP is followed by a period of increased excitability (supernormal period), then again by a prolonged period of reduced excitability (late subnormal period), before returning to resting excitability between 100 and 200 ms after the initial impulse, as determined in human motor axons by threshold tracking technique (Kiernan et al., 1996; Kuwabara et al., 2000).

The terms ARP and RRP only have well defined meanings with respect to single axons. A whole nerve trunk contains various fibers with different kinetics of

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recovery from refractoriness, leading to the distinction between ARP and RRP values corresponding to the fastest recovering fibers (ARPmin and RRPmin) and to the slowest recovering fibers (ARPmax and RRPmax). RPs can be determined in whole human nerves by paired pulses (PPs) applied at a single site, or by collision techniques, based on the stimulation of the same nerve trunk at two different sites. PP techniques use a first ‘conditioning’ pulse, delivered at supramaximal intensity to depolarize all motor nerve fibers, whereas stimulation intensity of the second ‘test’ pulse can be either supramaximal (Kopec et al., 1978) or adjusted to a percentage of maximal intensity (Kiernan et al., 1996). Collision techniques include a single pulse (Borg, 1980) or paired pulses (Kimura, 1976) at the proximal site of stimulation and a single pulse at the distal site, all pulses being delivered at supramaximal intensity. The double collision (DC) technique introduced by Ingram et al. (1987), include paired pulses at both sites of stimulation. The DC technique was found to be preferable to other collision techniques for clinical application (Ruijten et al., 1994a,b), notably because it allows the study of distal nerve fiber refractoriness.

The goal of this study was to compare the value of the DC technique and of two types of PP technique (with test pulse of supramaximal (PP^{supra}) or submaximal (PP_{sub}) intensity) to assess whole motor nerve RP distribution in healthy humans, using various methods of data analysis.

2. Methods

2.1. Subjects

The study included 32 healthy subjects, 13 women aged from 19 to 61 years (mean ± SD 29.6 ± 12.2) and 19 men aged from 20 to 55 years (32.5 ± 9.5). None of these subjects presented clinical or electrophysiological signs of peripheral nerve disorder. The experimental conditions were explained to all the subjects who gave their informed consent to participate to the study.

2.2. Stimulation techniques

Electrophysiological investigation was performed with a Phasis II machine (EsaOte Biomedica, Florence, Italy), using pre-gelled disposable surface electrodes (#9013S0241, Medtronic Functional Diagnostics, Skovlunde, Denmark) in all cases. The ulnar nerve was stimulated with pulses of 0.1 ms in duration, delivered either at a single site (wrist) for the PP techniques or at two sites (wrist and elbow) for the DC technique. The active electrode was placed over the ulnar nerve at wrist or elbow with the reference electrode at the dorsal aspect of the forearm (for wrist stimulation) or over the triceps brachii tendon (for elbow stimulation). The compound muscle action potentials (CMAPs) elicited by ulnar nerve stimulation were recorded from the abductor digitorum minimi (ADM) muscle. The active electrode was placed over muscle belly with the reference electrode on the metacarpus–phalanx joint. The signal was filtered through a 20–2000 Hz bandpass filter. CMAP amplitudes were measured from peak to peak.

First, the minimal stimulus intensity necessary to obtain a CMAP of maximal amplitude (Mmax) was determined for each site of stimulation. Supramaximal intensity was set at 15–20% above this value. For the DC technique (Fig. 1A), a paired pulse of supramaximal intensity with variable ISIs, ranging from 0.05 to 2 ms, was applied to the wrist. In addition, a paired pulse of supramaximal intensity with a fixed ISI of 4 ms (ISI of longer value than RRP) was applied to the elbow. The first pulses at the wrist and at the elbow were synchronized. The descending volley from the first wrist pulse was able to elicit a first Mmax. In contrast, the descending volley from the first elbow pulse collided with the antidromic volley of the first wrist pulse and did not elicit any response. When the second pulse at the wrist was delivered during the ARP (very short distal ISI), it could not collide the descending volley from the second elbow pulse, which could in turn elicit a second Mmax. In parallel with nerve fibers’ recovery from the ARP at the wrist, the amplitude of the response to the second elbow pulse decreased by collision. The ARPmin was defined by the distal ISI corresponding to the onset of this decrease, due to the fastest recovering fibers. The ARPmin defined by the distal ISI corresponding to the first occurrence of a response to the second wrist pulse was also determined. These two values of ARPmin were compared. The ARPmax was defined by the distal ISI corresponding to the complete collision of the response to the second elbow pulse, i.e. when the second pulse at the wrist was able to excite all motor nerve fibers, including the slowest recovering ones. By subtracting the Mmax obtained by a single supramaximal wrist stimulation from the global motor response elicited by the four pulses, the responses which resulted specifically from the second pulses delivered at the wrist and at the elbow could be determined for each ISI and were normalized to Mmax value.

For the PP techniques, two stimuli were applied at the wrist (Fig. 1B). The first pulse was of supramaximal intensity in all cases, while the intensity of the second pulse was set at the same intensity than the first pulse in the PP^{supra} technique and at the intensity required to obtain 50 ± 10% of Mmax in the PP_{sub} technique. The PPs were applied with variable ISIs, ranging from 1 to 4 ms. The Mmax produced by a supramaximal pulse was subtracted from the global response elicited by the PPs in order to analyze the specific response to the second pulse (Kopec et al., 1978), which was further normalized to Mmax value. The second pulse did not elicit any response if it was delivered during the ARP. In parallel with nerve fibers’ recovery from the ARP, the response to the second pulse increased in amplitude. The ARPmin was defined by