Clinical Neurophysiology 154 (2023) 27–33

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Strength-duration time constant and rheobase measurements: Comparison of the threshold tracking method and a manual procedure

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HIGHLIGHTS

- The strength-duration parameters derived by the threshold tracking method and by the manual procedure were strongly correlated.
- The median values of the strength-duration parameters obtained by the two techniques were not significantly different.
- There was no systematic bias of the manual procedure compared to the threshold tracking reference method.

ARTICLE INFO

Article history:
Accepted 29 June 2023
Available online

Keywords:
Rheobase
Strength-duration time constant
Threshold tracking
TROND protocol
QTRAC

ABSTRACT

Objective: To compare the strength-duration time constant (SDTC) and rheobase measurements obtained by the threshold tracking method (TT) and by a non-automated method (MM).
Methods: The MM procedure involved measuring, using a routine electrodiagnostic device, the intensity required to evoke a motor response whose amplitude corresponds to 40% of the maximum amplitude for four stimulus duration (1.0, 0.7, 0.5, 0.2 ms), and studying the linear relationship between stimulus charge and stimulus duration (slope = rheobase, intercept on the x-axis = SDTC). Using TT and MM, 30 successive healthy subjects (mean age = 38 years old) underwent a prospective evaluation of SDTC and rheobase of the median nerve motor axons at the wrist. Nerve stimulation and bipolar recording of evoked motor responses were performed with disposable self-adhesive surface electrodes.
Results: The Spearman correlations between the two methods were 0.78 ($p < 0.0001$) for SDTC and 0.96 ($p < 0.0001$) for the rheobase. The Bland-Altman analysis did not reveal any systematic bias of MM compared to TT.
Conclusions: The MM procedure was reliable for strength-duration relationship analysis.
Significance: We encourage neurophysiologists, who do not have dedicated threshold tracking equipment, not to hesitate to use these simple tools to assess peripheral nerve excitability.

1. Introduction

Historically, the study of the strength-duration relationship dates back to the early twentieth century, before the study of nerve conduction and skeletal muscles by needle-electrode. Notably, Lapicque and Weiss introduced the concepts of rheobase and chronaxie (Weiss, 1901; Lapicque and Lapicque, 1903). The strength-duration properties experienced renewed interest at the end of the twentieth century thanks to the work of Bostock and his collaborators (Bostock et al., 1994; Mogyoros et al., 1997b, 1998). Rheobase, which mainly reflects the passive properties of axonal membranes, corresponds to the current intensity (mA) required for an infinitely long current to reach the pre-established amplitude threshold of the motor response (mV). Chronaxie, or more precisely the time constant of the strength-duration relationship (SDTC), which mainly reflects the excitability of the nodal membrane, is the duration (μs) of a current whose intensity, to reach the pre-established amplitude threshold, is double the rheobase. Rheobase is typically increased in demyelinating neuropathies (Cappelen-Smith et al., 2001; Nodera et al., 2004) and remains unchanged in motor neuron diseases such as amyotrophic lateral sclerosis (ALS). In the latter, an increase in SDTC is usually described (Kanai et al., 2006; Vucic and Kiernan, 2006; Vucic and Kiernan, 2007; Mogyoros et al., 1998). Multifocal motor neuropathy with persistent conduction blocks (MMN) is part of the differ-

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https://doi.org/10.1016/j.clinph.2023.06.026
1388-2457/

ential diagnosis of ALS. In untreated MMN patients by intravenous immunoglobulin (IgIV), unlike ALS patients, SDTC is usually reduced (Priori et al, 2002). Kanai et al. (2012) have also established a relationship between the increase in SDTC in ALS and the reduced survival of these patients. SDTC is reduced in some chronic inflammatory neuropathies (CIDP) (Cappelen-Smith et al., 2001). Furthermore, in CIDP, Boërio et al. (2010) suggest that the immediate effects of IgIV are explained by their action on nodal persistent sodium currents, which account for the active component of SDTC (Baker and Bostock, 1997). The properties of the strength-duration relationship have also been studied in focal neuropathies such as carpal tunnel syndrome (Mogyoros et al, 1997a). More recent studies suggest such neurophysiological metrics may be used as pharmacodynamic biomarkers in pharmacological studies (Ruijs et al, 2022) and clinical trials (Mauricio et al, 2021).

Currently, the threshold tracking technique and its Trondheim (TROND) protocol, which allows the measurement of rheobase and SDTC of the strength-duration relationship, are internationally recognized as the gold standard for peripheral axonal excitability (Bostock et al., 1998). However, in this work, we wanted to find out if there was a reliable alternative for neurophysiologists who did not have dedicated threshold tracking equipment to use the parameters of the strength-duration relationship in their routine practice. Therefore, the objective of this study was to compare the measurements of SDTC and rheobase obtained by a manual procedure performed on a conventional electrodiagnostic machine (MM) with those obtained by the currently referenced method using threshold tracking (TT).

2. Material and methods

Thirty consecutive healthy subjects (mean age = 38 ± 12 years old; range: 23–66), 19 men and 11 women belonging to medical or paramedical staff as well as their family or friends, underwent a prospective evaluation of the SDTC and rheobase of the motor axons of the median nerve at the wrist using two distinct methods. None had clinical or electrophysiological signs of diffuse or localized peripheral neurological involvement, including carpal tunnel syndrome, and the usual risk factors for peripheral neuropathy (diabetes, alcohol or neurotoxic drug abuse) were excluded.

2.1. Recording and stimulating settings

The thenar muscles innervated by median nerve were studied with a standard device for studying motor nerve conduction. The ground, recording and stimulating electrodes were pre-gelled disposable surface electrodes (Spes Medica Srl, DENIB05026). The recording electrode (E1) was placed on the thenar eminence in close proximity to the muscle endplates halfway between the midpoint of the distal wrist crease and the first metacarpophalangeal joint. The reference electrode (E2) was placed over the dorsum of the proximal phalanx of the thumb. The ground electrode (E0) was placed on the ventral part of the forearm. The cathode was placed 2.5 cm proximal from the distal wrist crease along the course of the median nerve, and the anode 8 cm proximal from the cathode on the radial forearm. In accordance with Ohm's law (voltage = resistance × current or U = RI), skin impedances under the cathode, anode and ground electrode were systematically measured and kept near 5 kΩ or less by gently rubbing the skin with sandpaper, cleaning it with alcohol and rubbing it again with an abrasive and conductive paste. The wrist temperature was maintained above 31 °C using a heating splint specially designed for the study of nerve excitability (Fig. 1). This setup was positioned only once for both techniques.

2.2. Manual method (MM)

The data were collected using a Keypoint G3 EMG machine (Natus Medical Incorporated). The first step involved placing the self-adhesive electrodes to stimulate the median nerve and record evoked motor responses. Then, using the classic motor nerve conduction study (NCS) program included in the Keypoint software from Natus, similar to what is found in other electrodiagnostic devices from different brands, the maximum compound muscle action potential (CMAP) was evoked (bandpass filter setting: 2–5000 Hz), allowing the establishment of the target CMAP amplitude at 40% of the maximal motor response. Subsequently, using another preset page of the motor NCS program, the intensity required to reach the target amplitude (i40) was measured for four stimulus durations (1.0, 0.7, 0.5 and 0.2 ms). As the analysis was performed in the steepest part of the stimulus–response relationship, it was sometimes difficult to precisely reach the target amplitude (40% of the maximum motor response), as a change of 0.1 mA in stimulus intensity could result in a significant change in the evoked motor response amplitude. Preliminary studies have shown that the acceptable target amplitude range was from 37% to 43% of the maximum amplitude. More crucially for measurement accuracy, it was required that for each subject studied, across the four tested stimulus durations, the variability in target amplitude should not exceed 1% of the maximum amplitude (or 0.1 mV in absolute value). Then, by studying the linear relationship between stimulus charge (stimulation duration × intensity) and stimulus duration by inputting the four intensities values obtained in a predefined Excel page, the rheobase was defined by the slope of the linear relationship and the SDTC by the intercept on the x-axis (Fig. 1). This method was in accordance with Weiss's empirical law (Weiss, 1901) applicable to large-caliber myelinated axons: $Q = R(t + \tau)$, where Q was the amount of charge delivered, R was the rheobase, t was the stimulus duration and τ was the strength-duration time constant. Overall, between 40 and 100 stimuli were manually delivered, one at a time, to reach the target amplitude for the four stimulus durations, see the Supplementary Video.

2.3. Automated threshold tracking method (TT)

The measurements of SDTC and rheobase were performed using the TROND protocol within QTRAC software (© Institute of Neurology, University College London, UK) (Kiernan et al, 2000). The bandpass filter setting was set from 3 to 5000 Hz. Here also, the selected target response height was 40% of the maximal amplitude value and the intensity require to reach this amplitude was named the threshold. Two channels alternatively tracked on the one hand the threshold for a 1 ms test stimulus, on the other hand the threshold to a stimulus which was reduced in 0.2 ms steps from 1 ms down to 0.2 ms. Around 60 stimuli were automatically delivered at the frequency of 1 Hz.

The protocol was approved by the Belgian ethic committee (B7072022000001). Written informed consent was obtained from all participants.

2.4. Statistical analysis

The collected data included age, sex, height, weight, calculated body-mass index (BMI), stimulating electrode impedance, maximal CMAP and peak, SDTC and rheobase. Statistical analysis was performed by using SAS software (SAS University Edition, Cary, NC). For physical and demographic characteristics, descriptive statistics were expressed as means, standard deviations, minimal and maximal values. For excitability and technical data were expressed as quartiles (median, lower and upper quartiles). Given the small

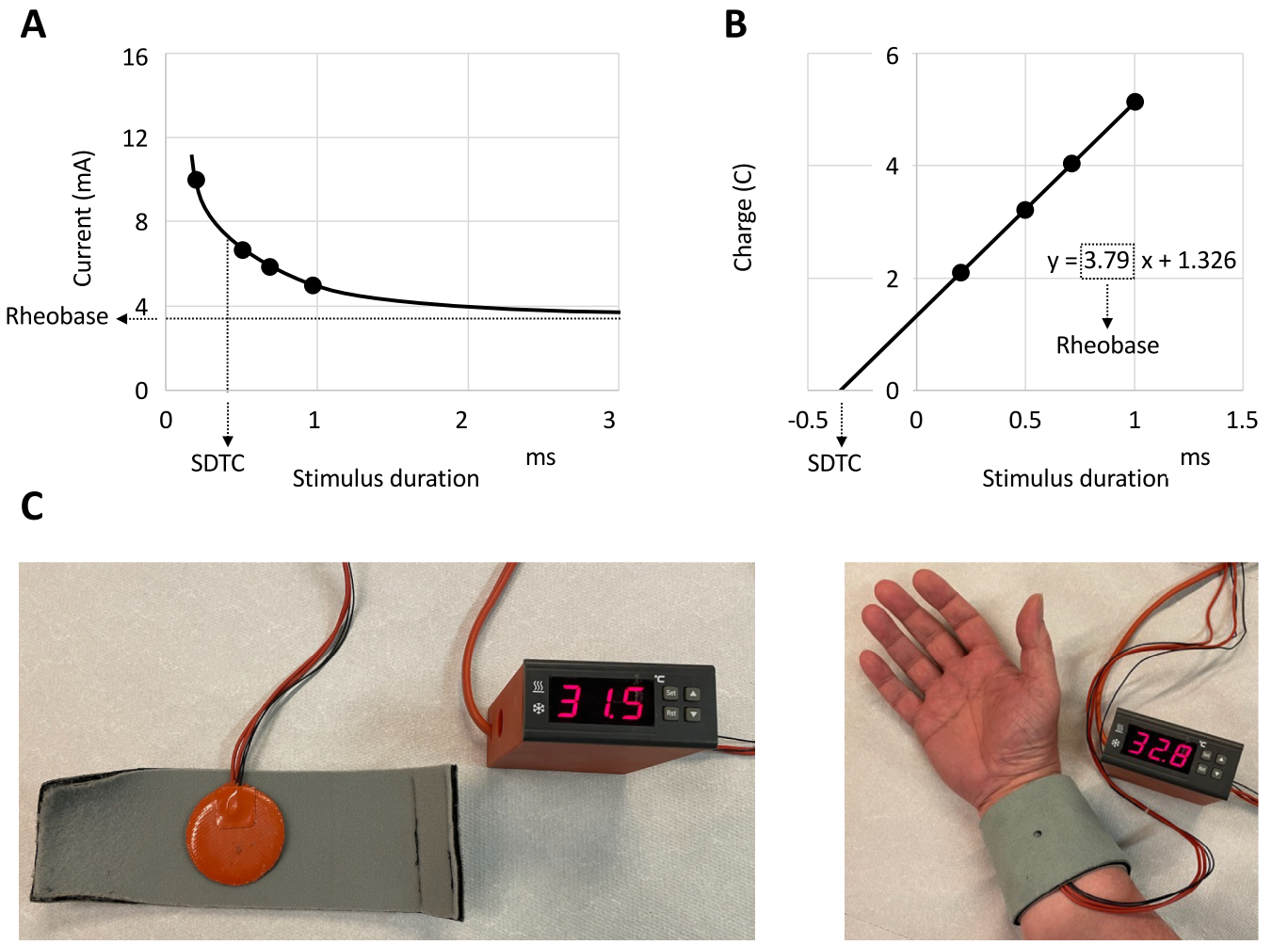

Fig. 1. Strength-duration relationship evaluated by the manual method.A. The intensity required to reach a target fixed at 40% of the maximal motor response amplitude was measured for four stimulus durations: 1.0, 0.7, 0.5 and 0.2 ms. The rheobase was the estimated threshold current for a stimulus of infinitely long duration. The strength-duration time constant (SDTC) was the minimum stimulus duration for a current twice rheobase. B. In practice, thanks to the empirical law of Weiss (1901), the curve in A was linearized by considering the relationship between the delivered charge (current × stimulus duration) and the stimulus duration. The rheobase was defined by the slope of the linear relationship (3.79 mA in this example) and the SDTC by the intercept on the x-axis (0.35 ms in this example). C. The wrist temperature was maintained above 31 °C using a splint with heating silicone (50 mm diameter), digital thermostat, 5 V/12 V transformer, and universal serial bus (USB) connection. This device was set up for both the manual method (MM) and the threshold tracking technique (TT).

sample size, and the fact that most of variables were not normally distributed according the Shapiro-Wilk test, only non-parametric tests were used: Spearman rank correlation coefficient and Wilcoxon signed-rank test for comparisons between data derived by both procedures. The existence of a systematic bias of the manual method compared to the automated method, considered as the reference procedure, was sought by the Bland-Altman analysis. A two-sided p value < 0.05 was considered significant.

3. Results

Table 1 shows the physical and demographic characteristics of the 30 healthy subjects, while excitability and technical data are presented in Table 2.

3.1. Correlation analysis

There were strong and significant ($p < 0.0001$) positive linear correlations between the data obtained by the two techniques ($n = 30$; $r = 0.78$ for SDTC; $r = 0.96$ for rheobase) (Fig. 2). The Spearman correlation matrix between all neurophysiological variables also revealed weak negative correlations between SDTC and rheobase: SDTC (TT) versus rheobase (TT) ($n = 30$; $r = -0.37$; $p < 0.05$), SDTC (MM) versus rheobase (MM) ($n = 30$; $r = -0.36$; $p < 0.05$). There was a strong and significant ($p < 0.0001$) positive correlation between peak (TT) and maximal CMAP (MM) of thenar muscles dependent on the median nerve ($n = 30$; $r = 0.67$). There were no significant correlations between stimulation electrode impedance and rheobase. Age and gender were also not significantly correlated with excitability parameters.

3.2. Bland-Altman analysis

The Bland-Altman analysis did not show any systematic bias of MM compared to TT. In fact, the 95% confidence interval for bias included zero for both rheobase and SDTC (Fig. 2).

3.3. Comparison analysis

The Wilcoxon signed-rank test between the data obtained from the two procedures did not show significant differences (Fig. 3).

The time required to obtain the values of rheobase and SDTC has not been precisely measured and compared, but it did not

Table 1
Physical & demographic characteristics (n = 30).

	Mean	Standard deviation	Minimal value	Maximal value
Age (years)	38	12	23	66
Weight (kg)	73.7	13.1	51	110
Height (m)	1.77	0.08	1.56	1.90
Body-mass index (kg/m^2)	23.5	3.16	18.3	30.8

Table 2
Excitability & technical data (n = 30).

	Median (Q2)	Q1	Q3
THRESHOLD TRACKING METHOD			
Peak (mV)	9.50	8.60	10.30
SDTC (μs)	455	390	490
rheobase (mA)	2.94	2.29	3.72
MANUAL PROCEDURE			
Maximal CMAP (mV)	9.35	8.10	10.70
SDTC (μs)	425	380	500
rheobase (mA)	3.01	2.34	3.72
STIMULATING ELECTRODE IMPEDANCE			
Anode (kΩ)	2.20	1.40	4.00
Cathode (kΩ)	2.00	1.30	3.40
Earth electrode (kΩ)	1.80	0.80	2.90

SDTC = strength-duration time constant; CMAP = compound muscular action potential; Q1 = lower quartile; Q3 = upper quartile.

exceed a few minutes for both procedures. The analysis of the strength-duration relationship consists of four steps:

- step 1, placement of electrodes for stimulation and detection of evoked motor responses: the duration of electrode placement was the same for both techniques, as designed in this study
- step 2, recording of the maximum motor response and determination of the target amplitude: this step took less than 30 seconds for the MM technique and slightly longer for the TT method (1 to 2 minutes) because the target amplitude was determined based on the stimulus–response relationship
- step 3, determination of the i40 for the four (MM) or five (TT) stimulus durations: this step took a little longer with the MM technique (1 to 2 minutes) compared to the TT method (approximately 1 minute)
- step 4, analysis time and obtaining the values of rheobase and SDTC: this step took less than a minute with the MM method because a predefined Excel sheet was used; the duration was slightly longer with the TT technique as it required exiting the acquisition program (QTRACS), filling in the "Legends and scaling" form, and opening the analysis program (QTRACP).

To illustrate these different steps of the MM method, a 2'-video is available as additional data to this article, see the Supplementary Video.

4. Discussion

The parameters of nerve stimulation, duration and intensity, are closely and inversely related. When the duration of the stimulus decreases, it is necessary to increase the intensity of the current. Conversely, when the duration of stimulation increases, the required current intensity decreases until the point where any further increase in the duration of stimulation no longer changes the necessary intensity to excite the studied nerve or muscle structure, which is called rheobase. When the rheobase is doubled, the required duration of the stimulus is reduced and corresponds to the chronaxie or SDTC (Fig. 1). In the present study and in other scientific studies (Mogyoros et al, 2000), the significative negative correlations observed between rheobase and SDTC are the translation of this close and inverse relationship between the duration and intensity of nerve stimulation.

Nerve excitability can therefore be studied by measuring rheobase and SDTC. In healthy subjects, it is possible to demonstrate the effect of polarization of axonal membranes on the parameters of the strength-duration relationship. Depolarization, induced for example by transient ischemia, increases SDTC and reduces rheobase (Kiernan and Bostock, 2000). We have already mentioned in the introduction of this article the numerous applications of the strength-duration relationship to diffuse or focal neuropathies and motor neuron diseases, as well as the interest of SDTC as a biomarker in pharmacological studies or clinical trials. The interest of strength-duration curves is therefore well established, but the question we raise in this study is whether it is legitimate and reliable to manually measure rheobase and SDTC on a conventional electrodiagnostic device.

The strong correlations between the parameters of the strength-duration relationship measured by automated (TT) and manual (MM) procedures, r = 0.96 for rheobase and r = 0.78 for SDTC; the absence of systematic bias of the MM technique compared to the reference TT technique indicated by the Bland-Altman analysis; and the absence of a significant difference between the medians of the parameters recorded by the two methods (Figs. 2 and 3) supported the reliability of the manual method (MM). However, TT offers an additional advantage for those who wish to refine the analysis of SDTC, namely the distinction between active and passive components using the latent addition technique (Bostock and Rothwell, 1997).

The device used in this study to maintain skin temperature above 31 °C (Fig. 1) probably did not play a decisive role in the strong correlation observed between the manual and automated procedures. Indeed, it has been shown that cooling (from 32 °C to 22 °C) had little effect on rheobase (12% reduction) and SDTC (18% increase) (Burke et al, 1999). However, even if the influence of cutaneous temperature on the strength-duration relationship is weak, temperature control is desirable especially if the analysis of peripheral axonal excitability includes more temperature-dependent tests such as the study of recovery cycle of nerve excitability after a supramaximal conditioning stimulus. (Kovalchuk et al, 2019).

The lack of correlation between the impedance values of the stimulating electrodes and the rheobase indicates that the care taken in preparing the skin, where the stimulation electrodes are attached, prevented impedance variability from affecting the results obtained. Under less rigorous examination conditions, in accordance with Ohm's law (U = RI), impedance variations would have had an impact on the recorded data, particularly on rheobase which should increase when the impedance itself increases.

Yerdelen et al (2006) found that SDTC was significantly higher in women than in men, and that in men, SDTC increased with age. The present study did not confirm these results, but the size of our sample (n = 30) was probably too small to demonstrate small differences statistically (n = 126 in Yerdelen et al's study).

The positive (r = 0.67) and significant (p < 0.0001) correlation between the peak measured by the TT method and the maximum

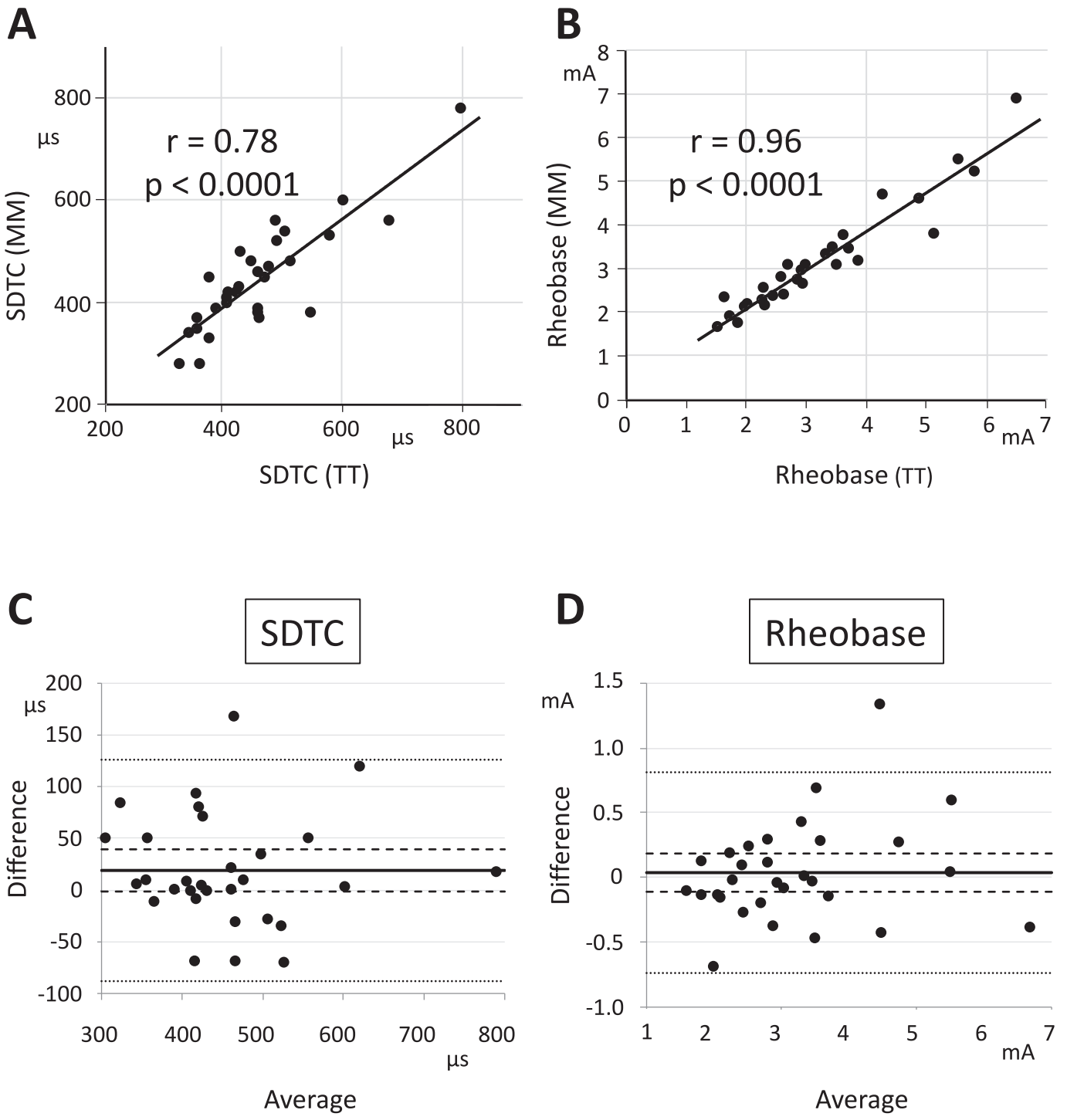

Fig. 2. Spearman correlations between the data obtained by the threshold technique procedure (TT) and the manual method (MM); and Bland-Altman plots.A. Strength-duration time constant (SDTC). **B.** Rheobase. The Bland-Altman analysis did not reveal any systematic bias of MM compared to TT for SDTC (**C.**) and rheobase (**D.**).

CMAP recorded by the MM method was expected, since these two parameters ultimately measured the same thing, the size of the maximum motor response. However, the correlation was not as strong as expected. The reasons for this relatively weak correlation were likely due to differences between the two techniques regarding nerve stimulation and recording of evoked motor responses: TT used a constant current stimulator increased in 2% increments, while MM used a constant voltage stimulator increased in potentially smaller increments (0.1% of the maximum stimulation intensity value); the algorithms used to measure motor responses were not necessarily identical; the "peak" parameter in TT corresponded to the average of three consecutive maximum peak values in the stimulus–response curve, while the maximal CMAP (MM) corresponded to an unaveraged maximum value obtained after a progressive increase in stimulation intensity. Lastly, there could have been a change in thumb or wrist position when transitioning between the two techniques.

These results suggest that both techniques can be used to assess the excitability of peripheral motor axons accurately, and their use will depend on researchers' preferences and the availability of

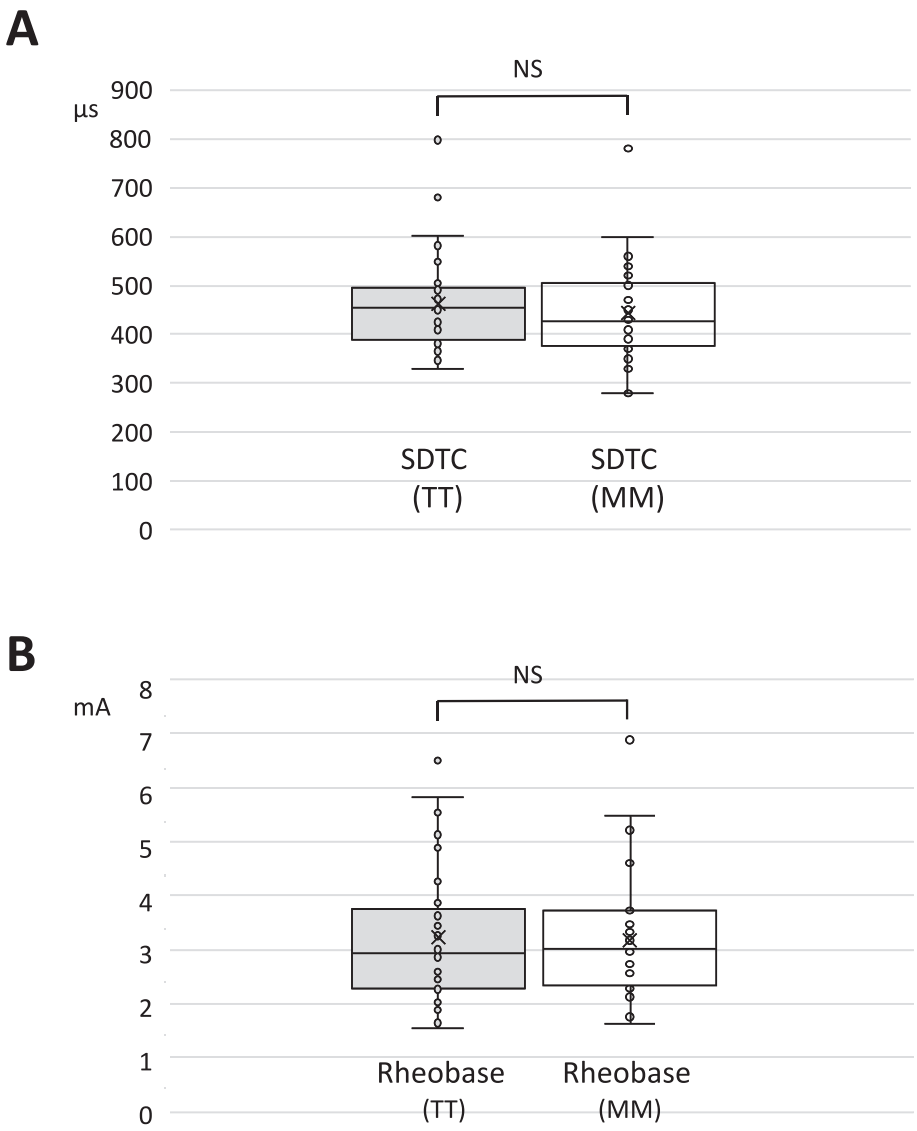

Fig. 3. Comparisons of data obtained by the threshold tracking procedure (TT) and the manual method (MM). The Wilcoxon signed-rank test between the strength-duration time constant (SDTC) and rheobase data derived from the two procedures did not show significant differences (NS).

measurement devices. However, further studies are needed to confirm these results and to evaluate the reproducibility and validity of MM in larger samples and other populations.

5. Conclusion

The manual establishment of rheobase and SDTC (chronaxie) as proposed in this study is reliable. Moreover, it is a fast procedure that takes no more than few minutes. Therefore, we encourage neurophysiologists not to hesitate to use these simple tools to assess peripheral nerve excitability.

Funding

Fonds De La Recherche Scientifique – FNRS. The threshold tracking equipment has been acquired through a scientific research investment fund: Fonds d'Investissements de Recherche Scientifique (FIRS) from the University Hospital of Liège (Belgium).

No role of study sponsor in data collection, analysis and interpretation and in drafting of the manuscript. If the study sponsors did not have such an implication.

Conflict of Interest Statement

None of the authors have potential conflicts of interest to be disclosed.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2023.06.026.

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