Recording cutaneous silent period parameters in hereditary and acquired neuropathies

Registro do período de silêncio cutâneo em neuropatias adquiridas e hereditárias

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Abstract

Background Cutaneous silent period (CSP) is the interruption in muscle activity after painful stimulation of a sensory nerve.

Objective The aim of the present study is to assess CSP changes in patients with polyneuropathy (PNP).

Methods The present study was carried out to assess CSP in individuals with diabetes (DM) and Charcot-Marie-Tooth (CMT) disease. The sample comprised 24 individuals with DM, 10 individuals with CMT1 disease, and 10 individuals with CMT2 disease. The control group (CG) consisted of 59 individuals.

Results The mean latencies recorded for the upper limbs in the CG were 79.2 milliseconds (onset latency), 69.3 milliseconds (50% reduction latency), 112.2 milliseconds (end latency), and 33.1 milliseconds (CSP duration). On the other hand, the mean latencies recorded for the lower limbs were 99.0 milliseconds (onset latency), 85.0 milliseconds (50% reduction latency), 136.9 milliseconds (end latency), and 38.2 milliseconds (CSP duration). The mean latencies recorded for the CG were significantly lower than the ones recorded for other groups, both in the upper and lower limbs.

Conclusions Cutaneous silent period values recorded for the CG in the present study were close to the ones reported in studies available in the literature. Abnormal CSP parameters were observed in the group of individuals with PNP. The end latency in the lower limbs helped differentiating the demyelinating subgroup from the axonal one.

Keywords
- Diabetes Mellitus
- Charcot-Marie-Tooth Disease
- Neural Conduction
- Diabetic Neuropathies
- Electromyography

Resumo

Antecedentes Período de silêncio cutâneo (PSC) é uma interrupção da atividade muscular após a estimulação dolorosa de um nervo sensitivo.

Objetivo O presente estudo tem como objetivo avaliar alterações do PSC em indivíduos com polineuropatia.

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Métodos O presente estudo avaliou PSC em indivíduos com diabetes mellitus (DM) e com doença de Charcot-Marie-Tooth (CMT). A amostra compreendia 24 indivíduos com DM, 10 indivíduos com CMT tipo 1 e 10 indivíduos com CMT tipo 2. Um grupo controle continha 59 indivíduos.

Resultados A média das latências do PSC registradas nos membros superiores no grupo controle foi 79,2 milissegundos (latência de início), 69,3 milissegundos (latência com redução de 50%), 112,2 milissegundos (latência final) e 33,1 milissegundos (duração do PSC). Por outro lado, a média das latências do PSC registradas nos membros inferiores foi 99,0 milissegundos (latência de início), 85,0 milissegundos (latência com redução de 50%), 136,9 milissegundos (latência final) e 38,2 milissegundos (duração do PSC). A média das latências registradas no grupo controle foi significativamente menor do que as registradas nos outros grupos (DM e CMT), tanto nos membros inferiores quanto nos superiores.

Conclusões Os valores do PSC registrados no grupo controle no presente estudo estiveram próximos aos reportados na literatura. Parâmetros anormais foram observados no grupo de indivíduos com polineuropatia. A latência final do PSC obtida nos membros inferiores ajudou a diferenciar os subgrupos desmielinizantes e axonais.

Palavras-chave
- Diabetes Mellitus
- Doença de Charcot-Marie-Tooth
- Condução Nervosa
- Neuropatias Diabéticas
- Eletromiografia

INTRODUCTION

Cutaneous silent period (CSP) is the momentary interruption of voluntary muscle activity; it is reflexively triggered after painful stimulation of a cutaneous sensory nerve.[1–5] It is an oligosynaptic nociceptive reflex that has been known for a long time.[1,4] Cutaneous silent period can be assessed based on the use of basic electroneuromyography equipment in the upper and lower limbs of individuals.[1,4,5] Scholars such as Kofler et al. have pointed out the need of enhancing the use of CSP assessment in routine electrophysiological evaluations.[6]

Most studies on CSP assessment have focused on investigating diseases affecting the central nervous system (CNS), whereas few studies have investigated CSP changes in peripheral neuropathies of different etiologies. Electrophysiological studies have been a useful tool in investigations about peripheral neuropathies. Electroneuromyography allows identifying, classifying, and quantifying peripheral nerve involvement in hereditary or acquired polyneuropathies; however, electrophysiological tests often assess large fibers in a more precise way during sensory nerve evaluations. Small, poorly myelinated type A-delta fibers and unmyelinated type-C fibers are not often assessed in most electroneuromyographic studies.[4,5] Some tests, such as CSP evaluation, can be implemented to assess the integrity of small fibers.[1–5,7] Some scholars have confirmed that CSP evaluation is a useful electrophysiological method to investigate the functions of small fibers.[1,3–5,7–9]

Cutaneous silent period evaluations performed in patients affected by peripheral neuropathies have shown abnormal results, mainly in diabetic individuals.[4,5,8–10] However, although some scholars take into consideration the CSP onset latency, others focus on latency when there is 50% reduction in muscle activity. Others even evaluate CSP duration. The aims of the present study were to evaluate CSP changes in patients with acquired and hereditary polyneuropathy (PNP) and to identify the most important CSP parameters used to assess peripheral neuropathies.

METHODS

Sample and ethical consideration

A cross-sectional observational study was conducted with a convenience sample to evaluate CSP in diabetic individuals, in patients with Charcot-Marie-Tooth disease (CMT) types 1 and 2, and in a control group comprising nondiabetic individuals without symptoms suggestive of PNP. Individuals presenting electrophysiological changes compatible with compressive neuropathies in the upper and lower limbs were excluded from the study. The research project was approved by the Research Ethics Committee of the Universidade Federal do Sergipe (CAAE protocol number: 48488115.0.0000.5546); all participants have signed the informed consent form.

Electrophysiological evaluation

Electrophysiological evaluation was performed in Viking Quest 10.0 equipment (Nicolet). Recordings were performed based on the recommended technique after thee limbs were warmed up to temperatures $> 33°C$. Action potential parameters such as distal latencies (DLs), action potential amplitudes (Compound muscle action potential-CMAP and sensory nerve action potential-SNAP) and conduction velocities of sensory and motor nerves were evaluated in the lower limbs and in at least one upper limb of the patients. Action potential amplitudes were measured from the negative wave peak to the baseline on motor nerves, as well as from peak to peak on sensory nerves. Posterior tibial, fibular, and median motor nerves, as well as sural sensory, superficial peroneal, and median nerves were assessed. Tibial and fibular nerves

were subjected to F-wave measurements. Criteria set by the American Association of Neuromuscular and Electrodiagnostic Medicine[11] were the ones used to classify axonal and demyelinated polyneuropathies.

Cutaneous silent period evaluation

Cutaneous silent period evaluation was performed in the upper limbs of the participants based on electrical stimulation of the median nerve and in their lower limbs based on sural nerve stimulation. Active uptake electrodes (E1) were attached to the thenar eminence in the upper limbs of the participants and the reference electrode (E2) was placed 2 cm distal to E1. Electrical stimuli were applied to the second finger of the participants, with square wave pulses of 0.5 milliseconds (in duration), at an intensity of 56 to 80 mA (from 14 times above the sensory threshold) and at a frequency of 3 Hz. Individuals were asked to perform maximum voluntary contractions during the electrical stimuli. Five recordings were made at 30-second intervals. Filters were set at 5 Hz to 10 KHz, the sweep duration was 250 milliseconds, and the sensitivity was 500 uV/division. Records were performed in overlapping rectified lines. Cutaneous silent period evaluation in the lower limbs of the participants was based on sural nerve stimulation. Active uptake electrodes (E1) were placed on their anterior tibial muscle and the reference electrode (E2) was placed 2 cm distal to the active electrodes. Electrical stimuli were applied to the distal third of the legs of the patients, lateral to the external malleolus, with square wave pulses of 0.5 milliseconds (in duration), at an intensity of 66 to 80 mA (from 14 times above the sensory threshold) and at frequency of 3 Hz. Individuals were asked to perform maximum voluntary contractions (dorsiflexion) during the electrical stimuli.[1,2,4,5,8]

The CSP parameters were defined after the aforementioned data were recorded. The CSP onset latency was defined as the full cessation of muscle activity. The CSP end latency was defined as the point when muscle activity resumed. The CSP duration was defined as the time elapsed from the beginning to the end of the electric silence. The moment when muscle activity amplitude reduced by 50% was also recorded (50% reduction latency).

Statistical analysis

Statistical analysis was performed in R software (R Foundation, Vienna, Austria) with a 95% confidence interval (CI) ($p < 0.05$). Continuous variables were expressed as mean and standard deviation (SD), whereas categorical variables were expressed as simple frequency and percentage. The Shapiro-Wilk test was used to check the adherence of quantitative variables to normal distribution. Thee means of each group were compared among each other through analysis of variance (ANOVA) and the Tukey test. The association between qualitative variables was investigated through the chi-squared test.

RESULTS

After application of the exclusion criteria, the final sample comprised 24 adult individuals with diabetes type 2 (mean age = 54.0 years old): 8 women and 16 men (DM group); 10 adult individuals with CMT1 disease (mean age = 34.2 years old): 8 women and 2 men (CMT1 group); and 10 adult individuals with CMT2 disease (mean age = 40.0 years old): 5 women and 5 men (CMT2 group). The control group (CG) comprised 59 individuals (mean age = 44.5 years old): 39 women and 20 men. Cutaneous silent period latencies were evaluated in the upper limbs of 43 individuals in the CG, in 9 individuals in the DM group, in 7 individuals in the CMT1 group, and in 7 individuals in the CMT2 group. They were also evaluated in the lower limbs of 21 individuals in the CG, in 20 individuals in the DM group, in 6 individuals in the CMT1 group, and in 9 individuals in the CMT2 group.

Among the variables (age, sex, and height) analyzed in the control group (CG), only height has influenced CSP onset and end latencies in the upper and lower limbs of the participants. None of the assessed variables influenced CSP duration. Almost all individuals in both CMT groups were classified as having moderate severity degree, based on the Charcot-Marie-Tooth neuropathy score (CMTNS).[12] ►**Table 1** shows the comparison of CSP latencies among all 4 assessed groups. The mean latencies recorded in the CG were significantly lower than those recorded in the other groups, both in the upper and lower limbs. The upper ($p = 0.250$) and lower ($p = 0.148$) limbs did not show significant difference in CSP duration.

When CSP was analyzed based on conventional electrophysiological evaluation results, it was possible to observe a significant difference in onset latency, in 50% reduction latency, and in end latency in the upper and lower limbs of groups of individuals with polyneuropathy (PNPG) and without it (NPNPG). There were no significant differences in CSP duration among groups (►**Table 2**). The CSP end latency showed a significant difference between the demyelinating (PNPd) and axonal (PNPa) subgroups, both in the upper and lower limbs. The other variables could not be used to separate the PNPa from the PNPd group.

DISCUSSION

The electrical stimulation of peripheral nerves induces short- and long-latency inhibitory and excitatory reflex responses.[3,6,8] One of these reflex responses results from the suppression of voluntary muscle activity – known as CSP – after high-intensity electrical stimulation in peripheral cutaneous nerves.[3,4,6,8] Although CSP has been known for a long time, it has been poorly applied in clinical practice.[6,7] It is an oligosynaptic reflex that happens at the spinal level, since the afferent pathway is composed of A-delta sensory fibers, whereas the efferent pathway is composed of thick alpha-motoneuron nerve fibers.[1–5,7,8]

Some scholars have investigated CSP behavior in healthy individuals and in patients with CNS-related diseases that can affect the modulation of interneurons during motor activities.[6] Cutaneous silent period changes have been mainly described in diabetic patients with peripheral neuropathies.[4–6,9] Initially, CSP using could help identifying impairments in small fibers that are not measured in

Table 1 Multiple comparison of silent period parameters between groups

Variable	CG	DM	CMT1	CMT2	*p-value*
Age (years old)	(34.2 ± 16.3)	(40.0 ± 10.8)	(54.0 ± 15.4)	(49.6 ± 39.7)	0.324
Sex (female)	39 (66.1%)	8 (33.3%)	8 (80.0%)	5 (50.0%)	0.020
CMTNS					
(mild/moderate/severe)	–	–	(1/9/0)	(1/8/1)	1.000
Median nerve					
Onset latency	(79.2 ± 7.5)^{A}	(96.4 ± 19.2)^{B}	(108.3 ± 22.1)^{B}	(104.0 ± 19.7)^{B}	< 0.001
50% reduction latency	(69.3 ± 7.7)^{A}	(87.8 ± 13.8)^{B}	(96.0 ± 19.9)^{B}	(89.3 ± 20.7 ^{B}	< 0.001
End latency	(112.2 ± 11.1)^{A}	(126.7 ± 13.0)^{A,B}	(156.2 ± 33.2)^{C}	(137.4 ± 16.5)^{C}	< 0.001
CSP duration	(33.1 ± 10.3)	(27.6 ± 9.5)	(47.8 ± 27.1)	(34.7 ± 10.6)	0.250
Sural nerve					
Onset latency	(99.0 ± 10.1)^{A}	(126.3 ± 16.2)^{B}	(138.0 ± 16.3)^{B}	(120.9 ± 14.9)^{B}	< 0.001
50% reduction latency	(85.0 ± 10.0)^{A}	(104.2 ± 17.2)^{B}	(115.7 ± 7.8)^{B}	(107.0 ± 9.1)^{B}	0.010
End latency	(136.9 ± 11.0)^{A}	(156.7 ± 13.6)^{B,C}	(173.8 ± 22.8)^{C}	(150.0 ± 19.5)^{A,B}	< 0.001
CSP duration	(38.2 ± 13.8)	(29.0 ± 17.7)	(41.4 ± 21.6)	(32.2 ± 12.8)	0.148

Abbreviations: CG, control group; CMT1, Charcot-Marie-Tooth Type 1 group; CMT2, Charcot-Marie-Tooth Type 2 group; CMTNS, Charcot-Marie-Tooth Neuropathy Score; DM, diabetes mellitus group.
Latencies in milliseconds. Letters A, B and C are results of the Tukey test: equal letters represent statistically similar means.

Table 2 Comparison between groups with and without polyneuropathy based on electroneuromyography

Variable	NPNPG	PNPG	*p-value*	PNPGa	PNPGd	*p-value*
Median nerve						
Onset latency	(79.2 ± 8.1)^{A}	(104.4 ± 19.5)	< 0.001	(100.8 ± 18.7)^{B}	(109.7 ± 20.8)^{B}	< 0.001
50% reduction latency	(69.9 ± 8.2)^{A}	(91.0 ± 17.6)	< 0.001	(87.6 ± 17.6)^{B}	(96.6 ± 17.8)^{B}	< 0.001
End latency	(112.7 ± 11.4)^{A}	(141.6 ± 24.7)	< 0.001	(132.8 ± 15.2)^{B}	(154.8 ± 30.9)^{C}	< 0.001
CSP duration	(33.2 ± 10.0)	(38.2 ± 15.5)	0.724	(32.6 ± 10.3)	(45.1 ± 26.2)	0.634
Sural nerve						
Onset latency	(99.4 ± 9.5)^{A}	(126.3 ± 17.4)	< 0.001	(123.8 ± 16.9)^{B}	(138.0 ± 16.3)^{B}	< 0.001
50% reduction latency	(85.0 ± 10.0)^{A}	(105.6 ± 14.1)	0.001	(103.8 ± 14.5)^{B}	(115.7 ± 7.8)^{B}	0.004
End latency	(139.4 ± 14.2)^{A}	(156.9 ± 18.0)	< 0.001	(153.8 ± 15.6)^{B}	(173.8 ± 22.8)^{C}	< 0.001
CSP duration	(39.8 ± 16.6)	(31.6 ± 15.6)	0.092	(29.5 ± 13.8)	(41.4 ± 21.6)	0.109

Abbreviations: ENMG, electroneuromyography; NPNPG, no polyneuropathy group; PNPG, polyneuropathy group; PNPGa, axonal polyneuropathy group; PNPGd, demyelinating polyneuropathy group.
Latencies in milliseconds. A, B and C are results of the Tukey test: equal letters represent statistically similar means.

conventional nerve conduction tests.[4,5,7,8] The present study has assessed several CSP parameters in diabetic patients and in individuals with axonal (CMT2) and demyelinating (CMT1) CMT disease. Cutaneous silent period evaluation has not been described in CMT patients, although this disease mainly affects large motor and sensory fibers.

Cutaneous silent period in healthy individuals was measured based on the recommended technique after sensory cutaneous nerve stimulation in the upper and lower limbs.[1,3–5,8] The present study was the first to analyze all CSP parameters, including onset latency, latency when muscle activity is reduced by 50%, end latency, and CSP duration. The values recorded for CSP latencies in the present study were close to the ones recorded in several studies available in the literature.[1,4–6,9,10] However, most of these studies have only observed CSP in the upper limbs of individuals and there was no standardization between them, since some of them considered CSP latency as the one that happens when muscle activity is reduced by 50%, whereas others considered CSP latency as the one that happens when there is full cessation in muscle activity.[1,4,5,8,9] This happens because scholars often use different CSP recording methodologies: some of them provide rectified records, whereas others provide unique records of CSP pathways.

The DM group presented longer latencies than the control group. It is worth emphasizing that most patients in the DM-group presented conventional electrophysiological changes compatible with PNP. It was also possible to differentiate

individuals with PNP – which was diagnosed based on electroneuromyography – from the ones who presented normal nerve conduction. This difference was more evident in the lower limbs than in the upper limbs. The CSP duration did not show a different behavior between the CG and the DM group. The findings of the present study are consistent with the literature, except for CSP duration, although the present research was the first to analyze all CSP parameters.

Lopergolo et al. have also evaluated CSP in individuals with PNPd and PNPa;[4] however, this classification was based on electrophysiological data, regardless of the etiology of the PNP. The aforementioned scholars recorded prolonged CSP latencies in individuals with PNP in comparison with healthy individuals, as well as a significant difference between the PNPd and PNPa groups. They used 50% reduction latency and only evaluated CSP in the upper limbs. The present study has also adopted the electrophysiological criterion; however, it has only investigated three causes of PNP, namely: diabetes, CMT1, and CMT2. Results have shown changed CSP in all individuals with PNP; the end latency analysis helped differentiating the PNPd subgroup from the PNPa one, both in the upper and lower limbs.

Only five individuals in the DM group presented conventional electrophysiology without signs of PNP. Only two of these individuals did not show CSP changes; however, only their upper limbs were evaluated. The study conducted by Onal et al. suggests that changes in CSP latencies and duration in the lower limbs of diabetic patients presenting normal conventional electrophysiology resulted from the involvement of small A-delta fibers.[5] Prolonged latencies were likely to be observed if the CSP evaluation had been conducted in the lower limbs of these two individuals. Diabetic neuropathy often affects large and small sensory fibers, although the small ones are harder to evaluate. Increased CSP latencies were already expected in diabetic individuals with abnormal electrophysiology; however, this outcome does not necessarily mean impairment in small fibers, since the efferent CSP pathway is composed of large fibers.[4] It is noteworthy that the diabetic individuals assessed in the present study presented neuropathic complaints that motivated the electrophysiological investigation; therefore, their peripheral nerves were likely to be already compromised. It would also be interesting assessing diabetic patients without neuropathic symptoms.

Individuals whose PNP was confirmed through electrophysiological examination have shown significantly increased CSP latencies in comparison to the ones presenting normal electrophysiology both in the upper and lower limbs. CSP duration was the only parameter that was not useful for this differentiation. End latency in the lower limb was longer in individuals with PNP. It was also capable of differentiating the demyelinating group from the axonal one. These data had not been previously described in the literature. Therefore, individuals with suspected peripheral neuropathy should be preferably assessed in the lower limbs.

Individuals with hereditary neuropathy have only shown a significant difference in end latency in the lower limbs between the PNPa and PNPd groups. It should be taken into consideration that large fibers are primarily compromised in case of CMT disease. If that was the case, changes observed in CSP could result mainly from the involvement of large fibers of the efferent pathway. Thus, one should evaluate the afferent conduction time to better understand to what extent small fiber impairment could affect CSP.

Cutaneous silent period values recorded in the CG in the present study were close to the ones reported in studies available in the literature, although these studies did not show standardization, and many of them used latency with a muscle activity reduction of 50%. Individuals whose PNP was detected through conventional electrophysiology presented abnormal CSP parameters, except for CSP duration. Cutaneous silent period assessment in the lower limbs has shown better results than the assessment conducted in the upper limbs.

The present study has some limitations, namely: it has evaluated individuals with PNPs that often compromise large fibers and that can compromise small fibers. Therefore, it is not possible to state that cases presenting prolonged CSP latencies also had impaired small fibers. It would have been necessary to assess the afferent conduction time and to calculate the conduction velocity of small fibers in order to evaluate them.

Authors' Contributions

ELAN: study design and conceptualization; major role in data acquisition; data interpretation; revision of the intellectual content of the manuscript; JRSS: data interpretation; revision of the intellectual content of the manuscript.

Conflict of Interest

The authors have no conflict of interests to declare.

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