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Original Article

Contact heat evoked potentials as a tool to study the lumbar region: normative data

José Geraldo Theml Batista Paraguassú Correia[1], Marco Orsini[2], Antonio Marcos da Silva Catharino[3], Bruno Lima Pessoa[4]

[1] Medical student at Federal Fluminense University, Niteroi – Rio de Janeiro/ RJ, Brazil.

[2] Severino Sombra University Center, Vassouras/ RJ, Brazil.

[3] Neurologist at Nova Iguaçu General Hospital, Professor at Iguaçu University - UNIG, Nova Iguaçu/ RJ, Brazil. Orcid: https://orcid.org/0000-0002-5736-1486

[4] Department of Neurology, Antonio Pedro University Hospital - Federal Fluminense University, Niteroi/ RJ, Brazil.

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ABSTRACT

Objective: This study aims to establish normal CHEPs data from the lumbar region.

Methods: Healthy subjects underwent CHEPs stimuli, being applied on lumbar (L1), and recorded in Cz and Pz, according to the standard technique. All the patients were divided by age and gender. We measured the influences of verbal rating scale (VRS) as well as age on N2-P2 amplitudes. Similarly, we tested the effect of height and age on N2 and P2 latencies. The 5th percentile for amplitudes and 95th percentile for latencies were also calculated.

Results: 36 patients were enrolled in this study. Only 1 out of 36 patient was excluded for not having recordable CHEPs. Differently from some studies, no impact of VRS and height was found on the variables N2-P2 amplitudes and N2 and P2 latencies, respectively. Although larger amplitudes and shorter latencies

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had been uncovered for females, no statistically significant differences were found. However, age was significantly correlated to N2-P2 amplitudes, N2 and P2 latencies over L1. Normative data was similar to the published for other centers.

Conclusion: we provided normative data for CHEPs usage in the study of lumbar pathologies. Age was the only element of influence in the CHEPs parameters

Significance: CHEPs may be regarded a valuable method to assess small fiber impairment in patients with lumbar pathologies.

Keywords: *evoked potentials, pain, heat stimulation, contact heat evoked potential*

INTRODUCTION

In the study and evaluation of pain fibers and their pathways, an ideal scenario would be a method that provokes a painful stimulus in a pain-specific manner; controlled, safe, and repeated that did not bring damage to the stimulated tissue. Although often used in the study of pain related to heat stimuli and thus the evaluation of thin fibers, laser evoked potential (LEPs) is based on the mechanism of small skin area stimulation (<5mm diameter). Doing so, it may not correspond to the reality of a skin stimulus evoked by heat naturally captured by larger extensions of the skin and its receptors. (Mor et al. , 1975, Chen et al. , 2001)

More and more used in studies of pain syndromes, contact heat-evoked potentials (CHEPs) has emerged as an effective electrophysiological evaluation method (Atherton et al. , 2007). In a practical way, it may be considered an equivalent somatosensory evoked potential for small fibers, evaluating the spinothalamic tract. Despite already exists diagnostic methods for assessing the thermal sensation and consequently fine fiber lesions; none are more objective for assessment of fine fibers than CHEPs. (Pralong et al. , 2004, Atherton et al. , 2007, Truini et al. , 2007)

Based on stimulation by heat, CHEPs can evoke brain potentials quite reliably. Releasing heat stimuli quickly, on the order of 70° C / s, a peak temperature is reached 360 ms after the stimulation, lasting 300 ms. Thus, it stimulates cutaneous nociceptors repetitively and in a wide

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area of skin, evoking brain responses based on the target temperature (Le Pera et al. , 2002, Lagerburg et al. , 2015). Hence, the signal is transmitted throughout C and A delta fibers to the central nervous system. Potential recorded by the A-delta fibers, with its highest point record in the vertex, results from the average cingulate cortex activation (Kakigi et al. , 2000, Valeriani et al. , 2002, Atherton et al. , 2007). Thus, electrodes placed on the vertex of the scalp can obtain evoked potentials, which permit a real evaluation of thermal nociceptive pathways (Chen et al. , 2001, Iannetti et al. , 2001, Atherton et al. , 2007, Cruccu et al. , 2008, Wydenkeller et al. , 2008, Haefeli et al. , 2013).

Moreover, it can be said that CHEPS is the brain response to a heat painful stimuli, and are strongly correlated with the perception of pain. In this regard, patients with neuropathic pain reveal a reduction in the amplitude of evoked pain potential. Latencies and potential amplitudes are strong and quite reproducible (Chen et al. , 2001, Valeriani et al. , 2002, Arendt-Nielsen et al. , 2003, Pralong et al. , 2004, Atherton et al. , 2007).

Nevertheless, the CHEPs amplitude and latency correlate with the verbal rating scale (VRS) of pain in healthy subjects: the higher the pain score, the lower the N2 latency and the greater the range N2-P2. This finding, in turn, may suggest the viability of nociceptive pathways (Le Pera et al. , 2002, Chao et al. , 2007). As a consequence, reduction of N2-P2 amplitude and increased potential latency may represent small fiber damage. Therefore CHEPS may show central nervous system activities that are affected by both peripheral deafferentation and changes in central pain processing (Valeriani et al. , 2002, Chen et al. , 2006, Chao et al. , 2008).

In clinical studies carried out by the concomitant use of CHEPS and skin biopsy, it has demonstrated a good correlation between both methods. That is, the greater the small fibers lesion, as evidenced by a lower density of epidermal fibers in the biopsy, the higher the latency, and the smaller the potential amplitude in CHEPS (Atherton et al. , 2007, Casanova-Molla et al. , 2011a, Casanova-Molla et al. , 2011b).

Despite the increased usage of CHEPS, there are still few studies regarding normative data

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of amplitudes and latencies for the lumbar region (Chen et al. , 2006, Lagerburg et al. , 2015, Granovsky et al. , 2016). Those data could allow critical studies in low back pain as well as any other condition from this region. Therefore, this study addresses CHEPs normative data to stimulation of lumbar spine, as well as assessing the variables of influence in the CHEPs parameters.

METHODS

Subjects

We analyzed 36 healthy volunteer individuals with a normal neurological examination, between 18 and 75 years old. There were 18 men (47,82 ± 17,01 years old, range 28-78 years) and 17 women (49,22 ± 16,78 years old, range 27-75 years). The age between both genders was not significantly different. No previous history of drug use, medications or diseases that predisposed to polyneuropathies, such as diabetes, amyloidosis, sarcoidosis, hepatitis, kidney failure or alcoholism was found. All data were collected prospectively. In order to obtain standardization of CHEPS data, we divided patients according to sex and age: 18-29 years (3 men, 3 women); 30-39 years (3 men, 3 women); 40-49 years old (3 men, 3 women); 50-59 years (3 men, 3 women); 60-69 years (3 men, 2 women); 70-79 years (3 men, 3 women). All the subjects according to the Helsinki Convention signed the consent form, and the hospital ethical committee approved the study.

Contact heat stimulation and recordings

All patients remained in supine position for evaluation of lower limbs and lateral position to evaluate the lumbar region during the exam. The room was kept in the average temperature of 22 degrees Celsius. All tests were performed in a quiet room, with the patient remaining comfortable during the exam. We asked all patients to maintain wakefulness during the test and avoid blinking, focusing on a predetermined imaginary point.

As standardization and prevention of cutaneous lesions, the maximum temperature reached during the stimulation was 51 degrees Celsius. All the patients were warned about the painful nature of the stimulus, although no skin lesion happens with the temperature employed. Using thermal stimulator contact (Medoc, Ramat

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Yishai, Israel), the lumbar spine (L1, spinous process) was stimulated.

Each stimulus was made in pulsatile fashion, lasting up to 12 seconds. Each one was made randomly moving the thermode around the member (and therefore in different locations), avoided the process of habituation of the painful phenomenon. Not least, the same gradation pressure with thermode on the skin was attempted during the examination performed for each stimulus.

Still, after each stimulus of 51 degrees Celsius with the thermode, we asked the patients for graduating the pain evoked by the CHEPS. We did that by using the VRS scale, whereas 0 meant no pain and 10 the worst pain possible.

The Stimulation parameters used were:

1. 51 °C, independent of the sense of responses of the subject and the characteristics of the waves.

2. Interval between stimuli (ISI) of 8-12s

3. Two stimulus series (10 stimuli each) for each body site; carried out in the affected dermatome according to previous clinical examination; order of random stimulation within the same dermatome.

4. At least 30s interval between two subsequent series.

5. Thermode was subtly moved horizontally after each stimulus without overlapping between two subsequent stimulation sites.

Statistical analyses

A p value lesser than 0,05 was used as statistically significant, rejecting the null hypothesis. By searching for normal distribution of a variable, Kolmogorov-Smirnov test was used. All the numerical data were revealed by mean ± SD since CHEPs latencies and amplitudes had a normal distribution. Chi-square or Fisher's exact test was used for comparing differences between nominal variables.

Aiming to evaluate gender differences, we divided females and males in two different samples, matched for height and age. After demonstrating no difference between these two groups, latency and amplitude were measured by unpaired t-test for the site stimulated (L1).

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Amplitudes N2-P2, as well as N2 and P2 latencies, were recorded at L1, as mentioned earlier. An independent physician performed and evaluated those CHEPS parameters. Since age, body height and VRS had normal distribution we measured the influence of age and VRS on CHEPs parameters by using N2- P2 amplitude as dependent variables in the multiple regression analyses and Pearson's correlation. In the same way, examining the influence of age and height on N2 and P2 latencies, the same type of analyses was made, considering the latencies as dependent variables.

Still, we estimated if there was any difference regarding the gender for recordable and not recordable CHEPs also by using Chi-square test. Since almost all latencies and amplitudes were influenced by age (and not by height), we calculated the normal limit of amplitudes by the mean expected and the 5^{th} percentile, to determine a cut-off. For latencies, we calculated the mean value and the 95^{th} percentile. As a result, amplitudes and latencies reference data could be calculated disregarding height.

As none of parameters were significantly different between female and male, those values were computed disregarding the variable gender and considering only age.

RESULTS

Subjects

Thirty-six subjects were enrolled for the study. In total there were 18 females and 18 males. One out of 36 subjects were excluded from this study for not having any CHEPs recordable, remaining 17 women and 18 men. The mean age was 48.54 ± 16.6 years. The average height was 168 ± 9.5 cm. There was no difference between male and female regarding age (p= 0.4) and height (p= 0.7). The mean VRS (visual rating scale) provoked by the CHEPs thermode was 6. In total, we were able to obtain CHEPs waveforms at L1 in 97,1% of patients (34 out of 35 patients). The mean N2 and P2 latencies were 424.6 ± 64.4 and 568.6 ± 80.3 ms respectively. The mean N2-P2 amplitude was 25.61 ± 11.6 μV. Table 1 shows the demographic and CHEPs data from the subjects.

Gender differences

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Since we did not find any difference between gender regarding age and height, we tested the influence of gender on CHEPs parameters. Doing so, no difference was found for N2-P2 amplitudes (p= 0.1), N2 latencies (p= 0.4) and P2 latencies (p= 0.2), concerning gender.

The influence of VRS and age on N2-P2 amplitudes

No significant effect caused by the variable VRS was found for N2-P2 amplitudes. However, age was negatively correlated to N2-P2 latencies (p= 0,01). This finding revealed a significant decrease on N2-P2 amplitudes, as individuals get older – figure 1.

Effects of age and height on N2 and P2 latencies

N2 (p = 0,003) and P2 latencies (p=0,02) were negatively influenced for the variable age (figure 2). Surprisingly, no effect on N2 and P2 latencies was found by the variable height. Altogether, these results showed a significant increase of N2 and P2 latencies across the lifespan.

Normal limits

Table 2 shows means, SD, upper normal limits (95^{th} percentile for latencies) and lower limits (5^{th} percentile for amplitudes) for all the CHEPs parameters. These values were calculated after stratification by age, disregarding gender (since there was no difference in amplitudes and latencies considering gender).

DISCUSSION

Understanding the pathophysiology of low back pain is of paramount importance given its prevalence and effects in quality of life. By providing normative values from the lumbar region, one could contribute to the study of diverse pathologies from this site. This may include low back pain (and other neuropathic pains from this site), traumatic spinal cord lesion, tumors and syringomyelia affecting the lumbar region. Since the method is versatile, one could use it in the study from any lumbar dermatome, in particular, depending on the level of the affection. Besides the diagnostic value of CHEPs, identifying the right level of lesion, tracking the response to any given treatment or monitoring signs of neurological deterioration may be some of the advantages of this method (Ulrich et al. , 2013).

All these information might also be critical in the context of surgical intervention, for example

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(Haefeli et al. , 2013). Since the majority of sensory function is evaluated by subjective measures, such as testing light touch and pinprick sensation (Maynard et al. , 1997), those evaluations could be better explored by using CHEPs, which provides more objective measurements throughout latencies and amplitudes (Jutzeler et al. , 2016).

Thus, few studies have evaluated the lumbar spine with the use of CHEPs. Given its proximity to the medulla, high CHEPs reproducibility rates in this region have been described (Selvarajah et al. , 2006, Parson et al. , 2013). Such characteristics place such method as promising in the study of painful conditions in this region (Parson et al. , 2013). Significantly, it is well known that some conditions, such as diabetes, may occur with early spinal cord involvement in the evolution of the disease, making it an ideal site for evaluation of peripheral nerve disorders (Selvarajah et al. , 2006). However, normative data should be acquired before using such method in the clinical scenario.

By recording CHEPs from L1, we were able to reproduce a significant amount of CHEPs waveforms (97,1%). Doing so, we obtained some normative data regarding N2 and P2 latencies, and peak-to-peak N2-P2 amplitudes. Characteristically, our mean L1 amplitude was lower (25.61 versus 44.93 μV) than Parson's et al. study (Parson et al. , 2013). However, our amplitude was similar to the data reported by Granovsky et al., who described 26.5 μV for women and 19.2 μV for men (Granovsky et al. , 2016). Regarding latencies, there were no discrepancies among our data and from other authors. Our mean N2 latencies were 424.6 ms (versus 407.03 from Parson's et al. study and 445.5 ms from the Granovsky's et al. study). Taken together, the latencies here found were characteristic of Aδ fibers (Chen et al. , 2001), with N2 peak latency around 500 ms.

Importantly, the differences regarding latencies and amplitudes may result from the stimulus temperature or from its duration (although we used the standardized temperature according to the CHEPs protocol) (Granovsky et al. , 2016). Still possible, different characteristics from the skin stimulated (thickness, hairiness, texture or even unknown skin proprieties from our population) may play a role in the different

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latencies and amplitudes found among the centers (Granovsky et al. , 2016).

Although not statistically different, there was a tendency for different CHEPs values regarding gender. This is according to Lagerburg et al., who found different amplitudes between males and females (Lagerburg et al. , 2015). A greater sample in our study could have overcome this lack of statistical difference for CHEPs data between male and female.

Similar to other studies (Lagerburg et al. , 2015, Granovsky et al. , 2016), both amplitudes and latencies were influenced by age. Significant negative correlation was found between age and N2-P2 amplitudes, with ager people showing lower amplitudes than the younger ones (fig.1). Inversely, N2 and P2 latencies were positively correlated to the age factor (fig.2). This represented an increment in latencies values as the age increased. The afferent input may be reduced secondarily to a neuronal loss, the aging brain or maybe any hypothetic peripheral nerve dysfunction resultant from the aging process. That pathophysiology could explain why the amplitudes and latencies correlate with the variable age in a significant manner (Gagliese et al. , 2000, Gibson et al. , 2001, Truini et al. , 2005). Since we stimulated each place no more than once at a time, we could assure that no habituation process occurred during the stimuli, which avoided this type of bias in our study.

Despite sufficient evidence has shown the correlation between the noticed pain intensity (by means of VRS) and the CHEPs amplitudes (Chen et al. , 2001, Atherton et al. , 2007, Casanova-Molla et al. , 2011a, Granovsky et al. , 2016), no significant effects on amplitudes were found in our study concerning VRS. Similar results were achieved by Chen et al. (Chen et al. , 2006). As these authors suggest, it is possible that there may be only an indirect relationship between pain-evoked potentials and peripheral nociceptive conduction (Chen et al. , 2006). Although conceptually regarded as a heat-evoked method and therefore painful, this was not a major issue in the study, with only a few patients complaining about the exam itself.

Realistically, as already stated for LEPS studies (Qiu et al. , 2002, Truini et al. , 2005), the significant interindividual difference, along with

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age and height decrement in CHEPS amplitudes, makes this parameter as one of limited usefulness. The exception could be if one find a unilateral alteration with normal contralateral CHEPs (Truini et al. , 2005).

Likewise, no relationship was seen between latencies and height. This finding contradicts what some papers have been shown, where a positive correlation between body height and latency in CHEPS may exist (Truini et al. , 2005, Chao et al. , 2007). However, results analogous to ours were also reported (Chen et al. , 2006), where no significant correlation between body height and latency was found. Despite some disparate results from different centers, taken together, the majority of studies agree with the variable age being a critical variable when considering amplitudes and latencies (Besné et al. , 2002, Chang et al. , 2004, Chen et al. , 2006, Chao et al. , 2007, Granovsky et al. , 2016).

The method (CHEPs) described here for evaluating patients with low back pain is easy, cost-effective and not time demanding, as already reported in some studies regarding other conditions (Wong et al. , 2011, Ulrich et al. , 2013). However, some limitations should be addressed. Although CHEPs is already well established as a reliable method in neurophysiology, it has only been used in the context of research and not in the clinical setting. One of its limitations relies on how one should interpret CHEPs amplitudes. This variable is subject to the influence of patient's attention in addition to the remarkable between-individuals variability (Beydoun et al. , 1993, Le Pera et al. , 2002, Jutzeler et al. , 2016). Therefore, is advisable to value only the variable latency, before more studies can clarify the role of amplitudes on CHEPs studies. Since we use fix temperatures of stimulation (as already standardized in CHEPs studies, 51° C) we may have misinterpreted the correlation between VRS and CHEPs amplitudes, assuming no correlation between those variables. This effect may be due to the different sensations under 51° C stimuli, with some individuals reporting unbearable pain and others do not. By adapting the temperature of the stimulus for each pain threshold may have solved this problem.

CONCLUSION

The present study provides normative CHEPs data

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in healthy subjects, from L1. The only factor regarded as influential in latencies and amplitudes was age. The normative data could be applied to diagnose a series of lumbar back pain affections, as well as to predict the prognosis of it. Importantly, CHEPs can be utilized to track the success of any treatment, such as conservative (e. g. drugs) or surgical ones. Nonetheless, new studies addressing this subject, with a larger population are demanding.

Table 1. Demographic and CHEPs data

Subjects	Gender	Height (cm)	Age	VRS	L1		
					N2	P2	N2-P2
1	F	178	29	7	408	564	26,45
2	F	157	27	3	402	506	24,95
3	F	160	28	1	402	550	44,99
4	M	171	28	6	394	570	36
5	M	172	41	3	422	542	16,01
6	M	176	29	4	416	578	22,01
7	M	186	28	2	422	606	17,03
8	F	160	37	1	402	520	12,22
9	M	170	65	4	458	570	5,72
10	M	164	60	8	436	598	13,93
11	F	170	30	7	386	506	49,93
12	F	165	32	7	386	542	34,7
13	M	190	30	2	408	534	29,48

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14	M	176	30	3	402	626	21,64
15	M	175	30	4	344	458	18,14
16	F	160	58	4	464	592	34,6
17	F	162	44	3	366	556	22,8
18	M	180	66	1	528	692	22,2
19	F	160	42	7	402	520	66,8
20	F	162	63	1	380	528	20,7
21	F	169	61	9	430	542	13,18
22	M	168	42	5	372	520	19,17
23	F	163	40	4	418	534	20,71
24	M	165	70	7	408	606	23,32
25	F	155	55	4	452	584	21,42
26	M	180	53	1	430	606	23,46
27	M	187	45	8	374	550	20,09
28	F	159	75	10	430	534	19,85
29	M	152	78	1	732	950	15,85
30	M	165	59	3	398	548	19,26
31	M	175	59	5	422	500	22,45
32	F	158	70	1	NR	NR	NR
33	F	160	71	1	430	534	15,56
34	F	160	70	1	478	626	11,34
35	F	170	54	8	436	542	5,98

N2= N2 latency (ms)

N2-P2= N2-P2 amplitude (μV)

NR = not recorded

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Table 2. N2-P2 amplitudes, N2 and P2 latencies as normative values found by age

Condition	Age	Mean (SD)	Normative percentile*
N2-P2 amplitude	18-29	25.01 (9.83)	17.03
	30-39	23.08 (5.80)	12.2
	40-49	18.42 (2.14)	16
	50-59	21.72 (2.19)	6
	60-69	19.58 (5.28)	5.7
	70-79	13.95 (8.24)	11.3
N2 latency	18-29	407.33 (10.25)	419.60
	30-39	388 (23.39)	405.60
	40-49	392.33 (24.8)	420.40
	50-59	433.67 (23.17)	459.20
	60-69	446.40 (53.8)	514
	70-79	495.60 (134.60)	681.20
P2 latency	18-29	562.33 (33.28)	594.80
	30-39	531 (55,19)	592,40
	40-49	537 (15,11)	553,60
	50-59	562 (39,39)	600,40
	60-69	586 (65,06)	673,20
	70-79	650 (172,78)	885,20

* 5^{th} percentile for amplitudes and 95^{th} percentile for latencies

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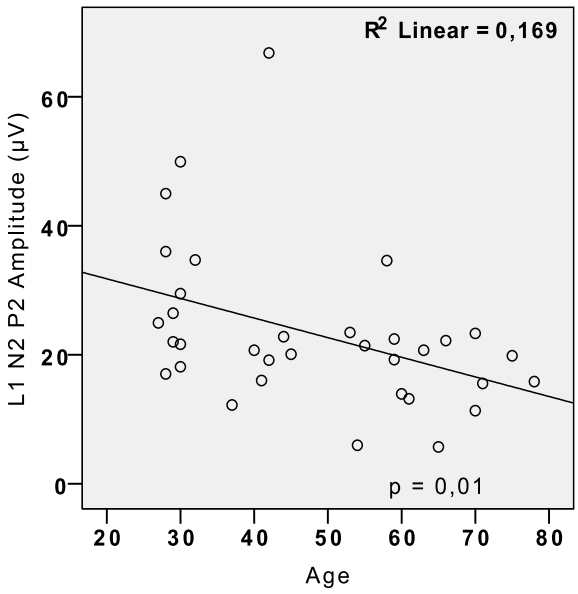
Figure 1. Negative correlation between amplitudes and age. No association between N2-P2 amplitudes and



VAS was found (not shown)

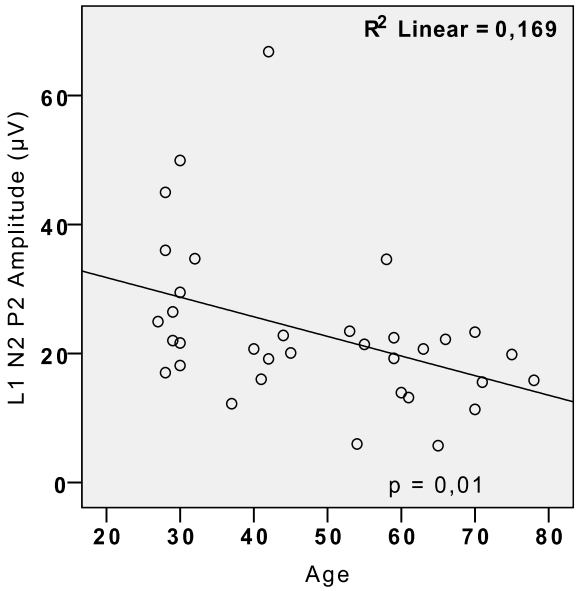
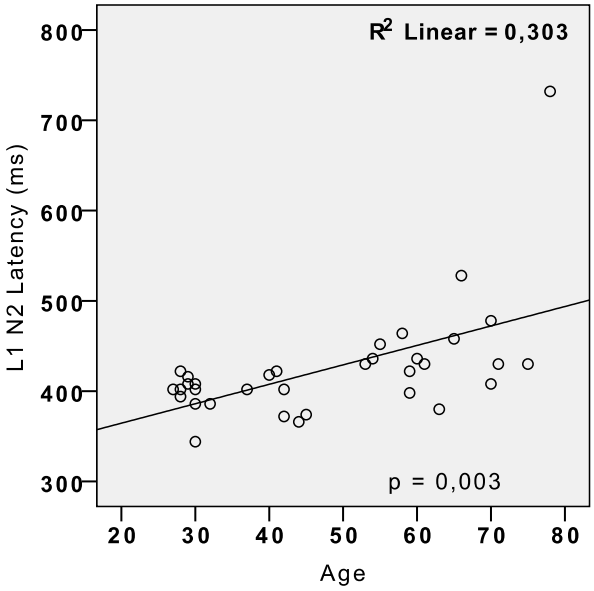
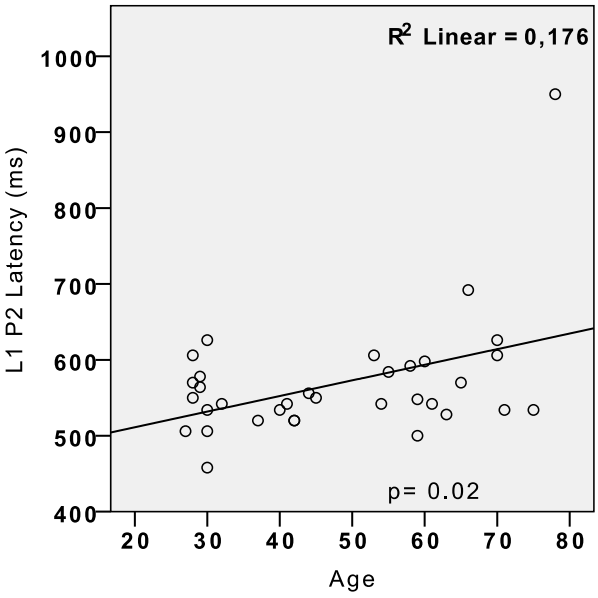


Figure 2. Correlation between latencies and age. Positive correlation was found between age and N2 latencies and age and P2 latencies. There were no correlation between height and latency (not shown).





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HIGHLIGHTS

Contact heat evoked potentials allow the assessment of Aδ and C fibers.

There is a lack of CHEPs data regarding the lumbar region.

Throughout CHEPs normative data, the identification of small fibers impairment in lumbar pathologies can be achieved and, therefore, a better understanding of the pathophysiology of low back pain may result.

DECLARATION: I declare that this article has not been published elesewhere.

Conflicts of Interest: Nil

REFERENCES

1. Arendt-Nielsen L, Chen A. Lasers and other thermal stimulators for activation of skin nociceptors in humans. Neurophysiologie clinique= Clinical neurophysiology. 2003;33:259.

2. Atherton DD, Facer P, Roberts KM, Misra VP, Chizh BA, Bountra C, et al. Use of the novel Contact Heat Evoked Potential Stimulator (CHEPS) for the assessment of small fibre neuropathy: correlations with skin flare responses and intra-epidermal nerve fibre counts. BMC neurology. 2007;7:21.

3. Besné I, Descombes C, Breton L. Effect of age and anatomical site on density of sensory innervation in human epidermis. Archives of dermatology. 2002;138:1445-50.

4. Beydoun A, Morrow TJ, Shen JF, Casey KL. Variability of laser-evoked potentials: attention, arousal and lateralized differences. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section. 1993;88:173-81.

5. Casanova-Molla J, Grau-Junyent JM, Morales M, Valls-Sole J. On the relationship between nociceptive evoked potentials and intraepidermal nerve fiber density in painful sensory polyneuropathies. Pain. 2011a;152:410-8.

6. Casanova-Molla J, Grau-Junyent JM, Morales M, Valls-Solé J. On the relationship between nociceptive evoked potentials and intraepidermal nerve fiber density in painful sensory polyneuropathies. PAIN®. 2011b;152:410-8.

7. Chang Y-C, Lin W-M, Hsieh S-T. Effects of aging on human skin

innervation. Neuroreport. 2004;15:149-53.

8. Chao C-C, Hsieh S-C, Tseng M-T, Chang Y-C, Hsieh S-T. Patterns of contact heat evoked potentials (CHEP) in neuropathy with skin denervation: correlation of CHEP amplitude with intraepidermal nerve fiber density. Clinical Neurophysiology. 2008;119:653-61.

9. Chao CC, Hsieh ST, Chiu MJ, Tseng MT, Chang YC. Effects of aging on contact heat-evoked potentials: The physiological assessment of thermal perception. Muscle & nerve. 2007;36:30-8.

10. Chen AC, Niddam DM, Arendt-Nielsen L. Contact heat evoked potentials as a valid means to study nociceptive pathways in human subjects. Neuroscience letters. 2001;316:79-82.

11. Chen I, Hung SW, Chen Y, Lim S, Tsai Y, Hsiao C, et al. Contact heat evoked potentials in normal subjects. Acta neurologica Taiwanica. 2006;15:184.

12. Cruccu G, Aminoff M, Curio G, Guerit J, Kakigi R, Mauguiere F, et al. Recommendations for the clinical use of somatosensory-evoked potentials. Clinical neurophysiology. 2008;119:1705-19.

13. Gagliese L, Melzack R. Age differences in nociception and pain behaviours in the rat. Neuroscience & Biobehavioral Reviews. 2000;24:843-54.

14. Gibson SJ, Helme RD. Age-related differences in pain perception and report. Clinics in geriatric medicine. 2001;17:433-56.

15. Granovsky Y, Anand P, Nakae A, Nascimento O, Smith B, Sprecher E, et al. Normative data for Aδ contact heat evoked potentials in adult population: a multicenter study. Pain. 2016;157:1156-63.

16. Haefeli JS, Blum J, Steeves JD, Kramer JL, Curt AE. Differences in spinothalamic function of cervical and thoracic dermatomes: insights using contact heat evoked potentials. Journal of Clinical Neurophysiology. 2013;30:291-8.

17. Iannetti G, Truini A, Galeotti F, Romaniello A, Manfredi M, Cruccu G. Usefulness of dorsal laser evoked potentials in patients with spinal cord damage: report of two cases. Journal of Neurology, Neurosurgery & Psychiatry. 2001;71:792-4.

18. Jutzeler CR, Rosner J, Rinert J, Kramer JL, Curt A. Normative data for the segmental acquisition of contact heat evoked potentials in cervical dermatomes. Scientific Reports. 2016;6.

19. Kakigi R, Watanabe S, Yamasaki H. Pain-related somatosensory evoked potentials. Journal of clinical neurophysiology. 2000;17:295-308.

20. Lagerburg V, Bakkers M, Bouwhuis A, Hoeijmakers JG, Smit AM, Van Den Berg SJ, et al. Contact heat evoked potentials: Normal values and use in small-fiber neuropathy. Muscle & nerve. 2015;51:743-9.

21. Le Pera D, Valeriani M, Niddam D, Chen AC, Arendt-Nielsen L. Contact heat evoked potentials to painful and non-painful stimuli: effect of attention towards stimulus

properties. Brain topography. 2002;15:115-23.

22. Maynard FM, Bracken MB, Creasey G, Ditunno JF, Donovan WH, Ducker TB, et al. International standards for neurological and functional classification of spinal cord injury. Spinal cord. 1997;35:266-74.

23. Mor J, Carmon A. Laser emitted radiant heat for pain research. Pain. 1975;1:233-7.

24. Parson HK, Nguyen VT, Orciga M-A, Boyd AL, Casellini CM, Vinik AI. Contact heat-evoked potential stimulation for the evaluation of small nerve fiber function. Diabetes technology & therapeutics. 2013;15:150-7.

25. Pralong E, Pollo C, Bloch J, Villemure JG, Daniel RT, Tétreault MH, et al. Recording of ventral posterior lateral thalamus neuron response to contact heat evoked potential in patient with neurogenic pain. Neuroscience letters. 2004;367:332-5.

26. Qiu Y, Inui K, Wang X, Tran TD, Kakigi R. Effects of attention, distraction and sleep on CO 2 laser evoked potentials related to C-fibers in humans. Clinical neurophysiology. 2002;113:1579-85.

27. Selvarajah D, Wilkinson ID, Emery CJ, Harris ND, Shaw PJ, Witte DR, et al. Early involvement of the spinal cord in diabetic peripheral neuropathy. Diabetes Care. 2006;29:2664-9.

28. Truini A, Galeotti F, Pennisi E, Casa F, Biasiotta A, Cruccu G. Trigeminal small-fibre function assessed with contact heat evoked potentials in humans. Pain. 2007;132:102-7.

29. Truini A, Galeotti F, Romaniello A, Virtuoso M, Iannetti G, Cruccu G. Laser-evoked potentials: normative values. Clinical neurophysiology. 2005;116:821-6.

30. Ulrich A, Haefeli J, Blum J, Min K, Curt A. Improved diagnosis of spinal cord disorders with contact heat evoked potentials. Neurology. 2013;80:1393-9.

31. Valeriani M, Le Pera D, Niddam D, Chen A, Arendt-Nielsen L. Dipolar modelling of the scalp evoked potentials to painful contact heat stimulation of the human skin. Neuroscience letters. 2002;318:44.

32. Wong MC, Chung JW. Feasibility of contact heat evoked potentials for detection of diabeticneuropathy. Muscle & nerve. 2011;44:902-6.

33. Wydenkeller S, Wirz R, Halder P. Spinothalamic tract conduction velocity estimated using contact heat evoked potentials: what needs to be considered. Clinical Neurophysiology. 2008;119:812-21.

Corresponding Author's: Bruno Lima Pessôa

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