Experimentally induced pain and paresthesia respond differently to cuff-based compression

Jacek Skalski[1*], Sylwia Swoboda[1], Tibor M. Szikszay[3], Piotr Wodarski[2], Andrzej Bieniek[4], Kerstin Luedtke[3] & Wacław M. Adamczyk[1,3]

[1]Laboratory of Pain Research, Institute of Physiotherapy and Health Sciences, Academy of Physical Education, Katowice, Poland

[2]Faculty of Biomedical Engineering, Department of Biomechatronics, Silesian University of Technology, Gliwice, Poland

[3]Institute of Health Sciences, Department of Physiotherapy, Pain and Exercise Research Luebeck (P.E.R.L.), Universität zu Lübeck, Lübeck, Germany

[4] Research & Development Department, "ARM Robotics", Katowice, Poland

***Corresponding author:** Laboratory of Pain Research, Institute of Physiotherapy and Health Sciences, Academy of Physical Education, Katowice, Poland

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Abstract

Neuropathic pain is a significant therapeutic challenge due to the co-occurrence with other neurological symptoms such as paresthesia. Human-based models e.g., cuff algometry, may provide a better understanding of the association between pain and paresthesia. This experiment aimed to characterize (psychophysically) pain and paresthesia evoked by stimuli of different temporal and intensity parameters and to demonstrate the reliability of experimental induction of these two symptoms using cuff algometry. Forty healthy participants were exposed to mechanical pressure stimuli at three intensities (100, 150, and 200mmHg) and three durations (90, 120, and 150s). Electrodermal activity (EDA) was continuously monitored, and participants rated pain and paresthesia in real-time using a computerized visual analog scale. General Linear Model analysis for paresthesia revealed significant differences among all durations ($p<0.01$), but not between all intensities as paresthesia did not increase from 150 to 200 mmHg ($p>0.05$). In contrast, for pain, significant differences were found across all pressure intensities ($p<0.05$) but not for all stimulus durations, as pain did not increase from 90 to 120, and from 120 to 150s ($p>0.05$). No interaction effects were observed for either symptom. EDA analysis showed no significant main or interaction effects. Intraclass correlation coefficients (ICCs) indicated that paresthesia and pain induction had moderate to good reliability across different durations and intensities (ICC: 0.52 - 0.90), while EDA showed poor to moderate reliability (ICC: 0.21 – 0.73). In conclusion, computer-based cuff algometry is an effective and reliable method to induce pain and paresthesia, allowing them to be assessed simultaneously. Furthermore, the results indicate that pain and paresthesia are characterized by different patterns, depending on pressure duration and intensity.

Keywords: experimental pain, cuff algometry, pressure, tingling, neuropathic pain, experimental model

1. INTRODUCTION

Neuropathic pain (NP) is a common clinical condition and accounts for a significant proportion of chronic pain in general [2,42]. The effective treatment of NP is a major challenge due to the complexity of the underlying pathophysiology and the limited efficacy of currently available treatments [5]. IASP defines NP as a pain that can arise as a consequence of lesion affecting the somatosensory system. However, the exact pathophysiological mechanisms, and the interaction between pain and other symptoms that co-exist with NP, are not yet fully understood.

Neuropathic conditions are accompanied by positive symptoms such as "paresthesia" [46]. According to the NINDS[1] definition, paresthesia refers to a burning or prickling sensation felt in different body regions and occurs during sustained nerve pressure. Paresthesia is a symptom frequently co-occurring with pain in conditions that involve nerve compression such as carpal tunnel syndrome [22,29] or radicular back pain [35]. However, paresthesia as a symptom may also co-occur with pain in common conditions such as fibromyalgia [45], migraine [3], or in patients with healed burns [7]. It is thus of highest importance to research beyond pain and characterize co-existing paresthesia because these two symptoms may affect each other, and treatment may be directed at both types of symptoms.

Cuff algometry may be utilized in human surrogate models of NP to simulate conditions of nerve compression and ischemia, thereby inducing ecologically valid sensations of pain and paresthesia. This method allows for the direct assessment of pain mechanisms and the efficacy of potential treatments through controlled stimuli and participant feedback [21]. Cuff-based algometry is a valid and reliable method to measure pain and tolerance thresholds [10]. Few studies targeted tonic ischemic stimulation with real time suprathreshold pain ratings (see [22, 38–40] for example). Although tourniquet based compression is a common method with a long history to induce paresthesia [9,34,41] or pain [38], there are only two studies that aimed to quantify paresthesia symptoms in nerve compression [15,32]. In both, paresthesia was not assessed parallelly to pain limiting direct characterization of these symptoms.

It remains unknown if the assessment of two symptoms characterizing NP is possible within a laboratory setting, and how these symptoms respond to transient ischemia induced by pressure of different parameters. This knowledge can enhance the understanding of the pathophysiology of NP and help to develop new diagnostic procedures and treatments. Thus, the main aim of this study was to offer a novel model to measure two symptoms simultaneously while monitoring skin conductance. To this end, induced pain was expanded by monitoring paresthesia in real-time. To test this model, stimuli with different intensities and durations were used to elicit pain and paresthesia. It was assumed that paresthesia develops gradually [16] because of the gradual development of hypoxia [28,44], whereas pain should follow the stimulus trajectory [40] and grow exponentially. Lastly, the experiment employed both

[1]National Institute of Neurological Disorders and Stroke

real-time and overall ratings and a test-retest design to test for reliability and agreement between the two methods of measurement.

2. METHODS

The experiment was conducted in the Laboratory of Pain Research at The Academy of Physical Education in Katowice in accordance with the recommendations of the Declaration of Helsinki. Each participant signed an informed consent before taking part in the study. The study protocol was approved by the local bioethics committee (decision no. 9/2019) and registered on the Open Science Framework platform (https://osf.io/wmhtq). All procedures were conducted by the same examiner (S.S).

2.1. **Participants and inclusion criteria**

A group of 40 participants (20 females, 20 males) were recruited from the University community by using social media advertisements and word-of-mouth. Only healthy pain-free (self-reported) individuals aged 18-35 were allowed to participate in the study. A screening questionnaire was used to exclude those individuals who had any medical condition that could have influenced pain perception, such as neurological diseases or upper limb pain, lasting more than 24h within the month preceding the study, had any systemic disease or the history of intolerance to ischemic stimuli during routine blood pressure measurement. To standardize the side of the body exposed to ischemic stimuli, only right-handed participants were included. Before signing the informed consent, participants were informed about the study procedures and that they can withdraw from the study at any moment without any consequences and reason for a withdrawal.

2.2. **Study design**

The study employed a within-subject design. Participants received three intensities of mechanical pressure stimuli (100, 150, 200mmHg) applied with three different durations (90, 120, 150s) in two sessions which resulted in nine stimuli during the first session and nine during the second session (18 stimuli in total). Random sequences of parameters were generated for each session. During each stimulus, subjects rated both symptoms (pain and paresthesia) simultaneously in real time and additionally provided overall ratings after each stimulus.

2.3. **Experimental procedure**

2.3.1. **Equipment**

To induce pain and paresthesia, a commercially available sphygmomanometer's cuff (Omron M3 HEM-7200-EE2(V), Omron Healthcare Co., Ltd., Japan) was adapted and paired with sliding potentiometers to rate the symptoms on Computerized Visual Analogue Scales (CoVAS) in real-time. Skin conductance was measured using electrodermal activity (EDA) and continuously recorded via a USB coupler device (USB Physiology Coupler Contact Precision

Instruments®, Pendragon House, Butleigh Rd, UK) connected with two 8mm diameter Ag-AgCl cups filled with EDA gel (EDALYT, EasyCap GmbH, Germany) attached to the distal phalanges of non-dominant index and middle finger. The experiment was programmed and carried out using the PsychoPy (v2021.2.3) open-source software [36]. Two Python libraries ("serial" and "u3") were used to control the cuff, potentiometers, and digital/analogue converter LabJack U3-LV device (LabJack Corporation, Lakewood, CO, USA) which was used to ensure communication with the EDA device.

2.3.2. **Preparation**

Participants were seated on an armchair next to the computer screen with arms resting on a table. After completing the screening questionnaire and signing the informed consent, age, height, weight and arm circumference (measured with a measuring centimeter at the widest point of the arm, near the mid-length of the humerus) were collected. Additionally, participants were asked to rate their fear of pain on a 0-10 Verbal Rating Scale (VRS) where 0 indicated "no fear of pain" and 10 indicated "very high fear of pain". A sphygmomanometer cuff was placed on the participant's left arm, just above the elbow joint (flexed at 90° angle). The phalanges of the index and middle finger were previously prepared by washing the hands with lukewarm water [5]. Two electrodes were attached using self-adhesive tape. The examiner explained how to operate the potentiometers to reflect intensity of both, pain and paresthesia before the data collection was started.

2.3.3. **Familiarization trial**

After the cuff was fitted, one test compression (150mmHg) was performed to familiarize the subjects with the modality of the stimuli and the assessment procedure. Participants were asked to maintain a relaxed position during the test, minimize movement of the tested limb (left), and assess the intensity of pain and paresthesia in real time (using their right hand) on the sliders placed in front of them.

2.3.4. **Measurement and outcomes**

Following the familiarization trial, the main phase of the experiment started. It consisted of two series of nine stimuli each (60s interval between trials). The stimuli were presented in a random order, unbeknownst to the participants and the examiner, and each parameter was applied twice per subject for a total of 18 compressions to allow for reliability analysis. A 15-minute break between the first and second series included removing the compression cuff and encouraging free limb movement to stimulate blood circulation. The second series was identical to the first. Participants assessed pain and paresthesia intensity in real-time using the CoVAS by maneuvering potentiometers. After each trial, they rated overall pain and paresthesia on a VAS scale displayed on the computer screen. Main outcomes included pain and paresthesia intensity for different compression intensities and durations,

measured on the CoVAS scale. The EDA signal was continuously recorded throughout the experiment, with each stimulus onset and offset digitally marked. Demographic data (sex, age, weight, height) and arm circumference were collected to characterize the sample and assess correlations with pain and paresthesia severity. Quality of reported pain was also recorded.

2.4. **Data processing and statistical analysis**

Raw data from CoVAS were first imported and preprocessed by using MATLAB R2023b (MathWorks, Natick, MA) prior to the main statistical analyses. Continuously measured pain and paresthesia intensity as well as stimulus data (pressure) were first reduced at the subject level by averaging ratings for each second of data acquisition. Reduced data were then plotted as a time-function and used to calculate mean ratings for each applied stimulus as well as Areas Under the Curve (AUC) for each of the 2 sessions. To correct for the delay in establishing a target level of pressure, parameters (mean, AUC) were calculated based on the data from the plateau phase of each stimulus. The electrodermal activity (EDA) signal was first smoothed with the moving average and later encompassed with similar preprocessing steps as the behavioral data described above.

Descriptive statistics are presented as means and standard deviations (SDs) unless otherwise indicated. The main analysis was performed by means of the General Linear Model (GLM) for repeated measures, with two within-subjects factors, i.e., stimulus intensity (pressure of 100, 150, 200mmHg) and stimulus duration (90, 120, 150s). Primary analysis was performed on the extracted means from curves instead of AUC to be able to analyze the effect of two factors (time and stimulus intensity) independently due to relative dependency of AUC values from both reported symptoms and duration of exposure. Post-hoc Tukey tests were performed in case of statistically significant main and/or interaction effects. Furthermore, reliability of measurement was calculated by using Intraclass Correlation Coefficient ($ICC_{(3,1)}$) and Smallest Detectable Differences (SDDs) to reflect the correlation between the data from the first session vs. second session. Reliability was interpreted as excellent (0.9-1), good (0.75-0.9), moderate (0.5-0.75) or poor (<0.5) [24]. Preliminary concurrent validity was analyzed by applying Pearson-product moment correlation coefficient and correlating overall ratings collected after application of the stimulus with corresponding averaged ratings derived from continuously measured symptoms: pain and paresthesia. Bland-Altman plots were used to further visualize systematic differences between two methods and explore bias in datasets from two sessions; 95% Limits of Agreement (LoA) were calculated.

3. RESULTS

Descriptive statistics are presented in **Table 1**, whereas means and standard deviations for all experimental conditions and outcomes are presented in **Table 2**. Averaged outcomes measured over-time and stimulus data are shown on **Figure 1.**

Table 1. Descriptive statistics

Variable	Mean	SD
Participant characteristics		
Age [years]	21.10	1.72
Body mass [kg]	72.06	14.36
Height [cm]	174.15	8.69
Arm circumference [cm]	28.85	4.06
Sex [% of females]	50%	
Psychological measures		
Fear of pain [VRS]	3.28	1.69

Legend: Fear of pain was measured on 0 – 10 Verbal rating Scale (VRS) scale (0 – no fear of pain; 10 - the worst fear of pain imaginable).

Table 2. Means and SDs for all conditions and outcomes

Duration [s]	Intensity [mmHg]	Paresthesia Mean (SD)	Pain Mean (SD)	EDA Mean (SD)
90	100	4.40 (6.11)	6.66 (9.30)	2.74 (1.57)
	150	5.60 (7.62)	11.11 (13.56)	2.71 (1.71)
	200	7.29 (9.76)	22.54 (19.62)	2.84 (1.95)
120	100	6.75 (8.84)	7.31 (9.08)	2.68 (1.54)
	150	7.80 (8.61)	12.42 (13.53)	2.69 (1.59)
	200	9.72 (9.26)	22.87 (18.05)	2.67 (1.59)
150	100	9.60 (9.21)	8.06 (10.70)	2.60 (1.58)
	150	14.11 (12.01)	13.57 (13.65)	2.63 (1.60)
	200	12.58 (10.43)	24.73 (17.62)	2.75 (1.69)

Legend: Condition i.e., 90/100 indicates condition where pressure stimulus had a duration of 90 seconds and intensity of 100 mmHg; SD – Standard Deviation; EDA- electrodermal activity.

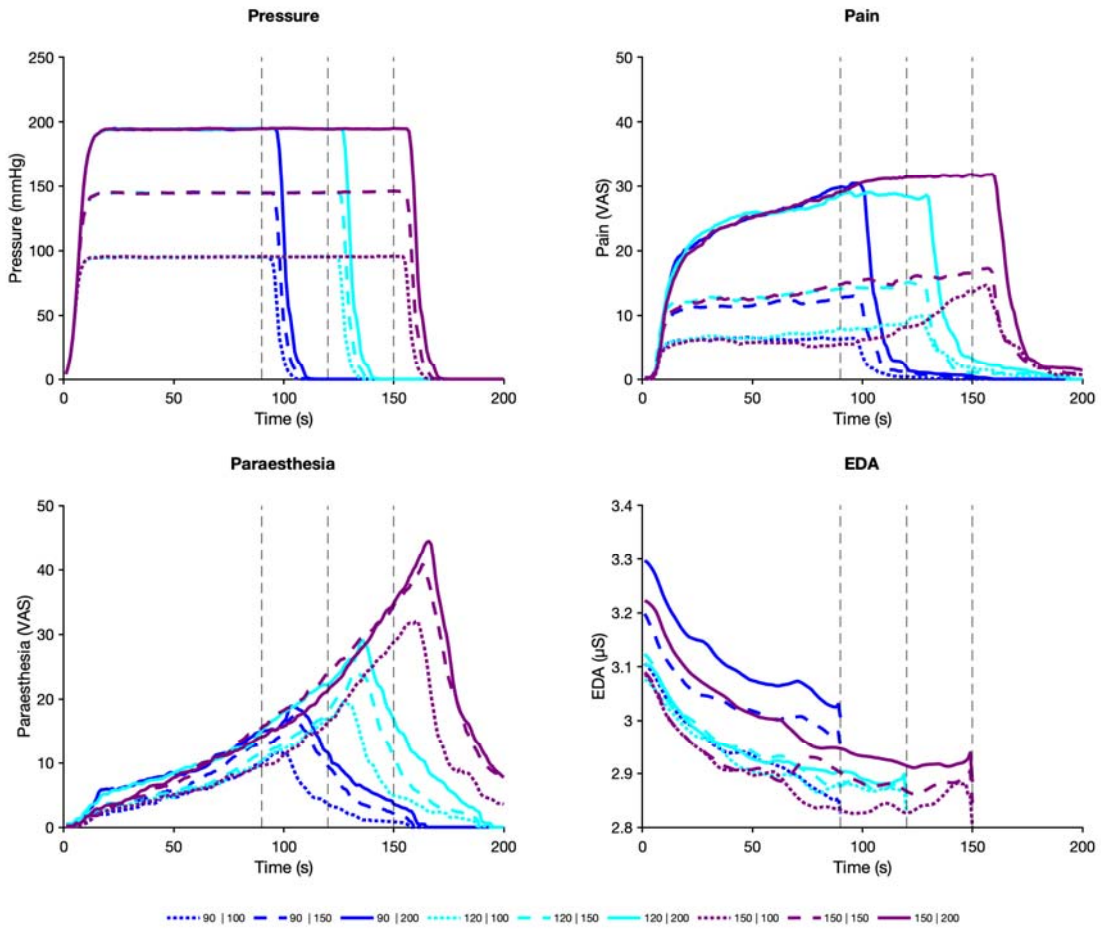

Figure 1. Main outcome measures and stimulus data collected in real time. The upper left panel represents the pressure (mmHg) from each stimulus type. Upper right panel reflects mean pain scores, lower left mean paresthesia scores, lower right mean EDA values in µS. Each line represents a different stimulus. Colour (blue, cyan, purple) represents stimulus duration (90, 120, 150s.), line type (dotted, dashed, continuous) represents stimulus intensity (100, 150, 200mmHg). Vertical markers indicate stimuli offsets.

Primary analyses reported below were conducted on average perceived pain and paresthesia intensity, however, they were repeated also with AUC as an outcome and are presented separately in the **Appendix**.

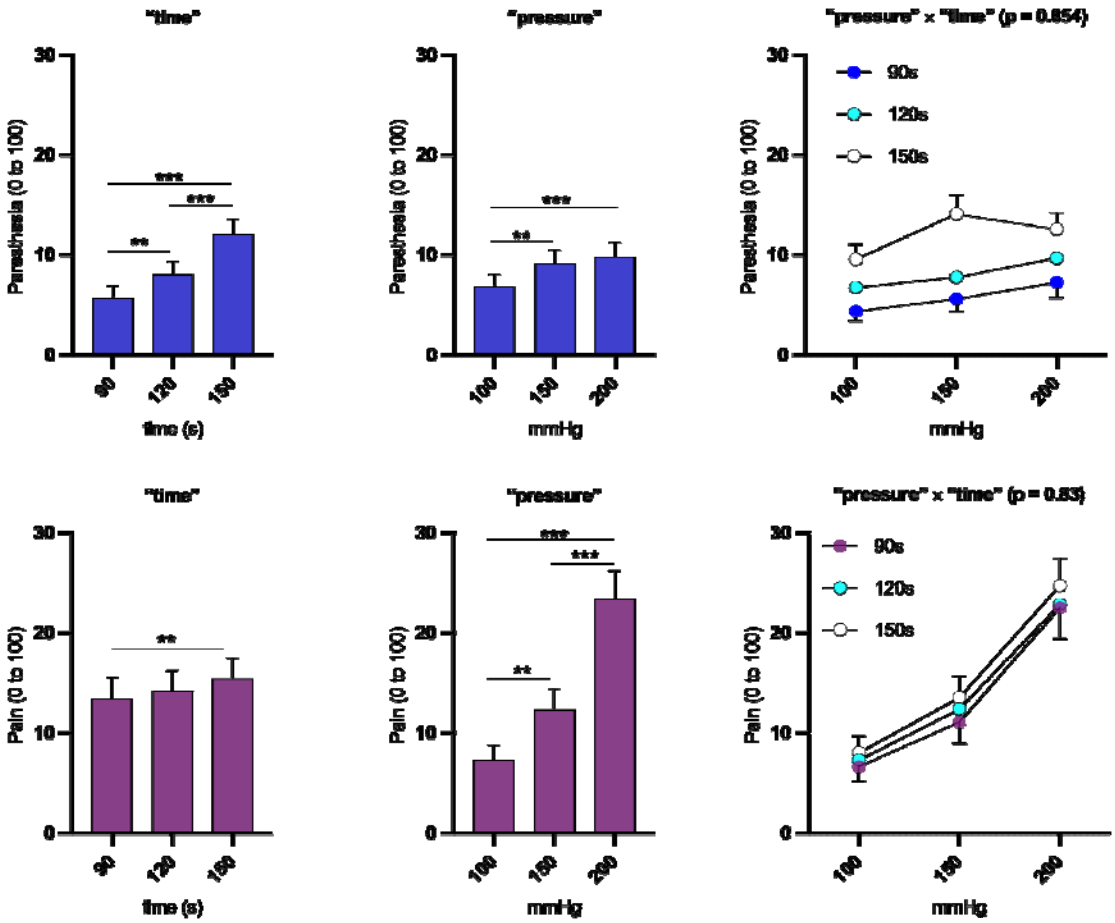

Figure 2. Main and interaction effects. Upper panel shows the average values of perceived paresthesia for each stimulus duration (upper left) and intensity (upper middle) and interaction effects (upper right). Steven's power law function fitted to the data show exponent >1 for the relationship with duration (1.52) and exponent < 1 for the relationship with pressure (0.50) indicating exponential and logarithmic relationship, respectively. Reversed relationships were found in pain (Lower panel): exponential was relationship with pressure (1.86) and logarithmic saturation with duration (0.27). Legend: CoVAS – Computerized Visual Analogue Scale; mmHg – millimetres of mercury.

3.1. *Paresthesia*

The GLM analysis revealed statistically significant main effects for "time" ($F_{(2, 78)} = 37.34$, $p < 0.001$, $\eta^2_p = 0.49$) and "pressure" ($F_{(2, 78)} = 8.45$, $p < 0.001$, $\eta^2_p = 0.18$), indicating that paresthesia depended on duration as well as on intensity of the stimulus (but to a lesser extent: $\eta^2_p = 0.49$ vs. $\eta^2_p = 0.18$). Post-hoc comparisons revealed statistically significant differences between all three durations (90s vs. 120s, 90s vs. 150s, 120s vs. 150s), however, interestingly, in case of stimulus intensity (pressure) differences were significant only between 100 vs 150 mmHg and 100 vs 200 mmHg, but not between 150 mmHg vs 200 mmHg. No interaction of "pressure" × "time" factors was observed ($F_{(4, 156)}=2.37$, $p=0.55$, $\eta^2_p = 0.06$) (see **Figure 2**).

3.2. *Pain*

The GLM analysis for pain also revealed statistically significant main effects for the factors "time" ($F_{(2, 78)} = 7.28$, $p < 0.05$, $\eta^2_p = 0.16$)) and "pressure" ($F_{(2, 78)} = 63.02$, $p < 0.05$, $\eta^2_p = 0.62$). But contrary to paresthesia, *post-hoc*

comparisons revealed statistically significant differences between all pressure intensities, however, in the temporal domain, significant differences were found only between the shortest and the longest time duration (90 vs. 150s). No interaction of "pressure" × "time" factors was observed ($F_{(4, 156)}$=0.37, p=0.83, η^2_p = 0.009 (**Figure 2**).

3.3. *Electrodermal activity*

Data from ten participants were excluded from analysis due to missing signal recordings in the first (n = 4) or second (n = 2) session of the experiment or abnormal signals (n = 4) as the result of device malfunction during data acquisition. The GLM analysis applied to EDA data did not show statistically significant effects for "time" ($F_{(2, 58)}$ = 0.86, p = 0.43, η^2_p = 0.03), "pressure" ($F_{(2, 58)}$ = 0.99, p = 0.38, η^2_p = 0.03) and "time" × "pressure" interaction ($F_{(4,116)}$ = 0.31, p = 0.87, η^2_p = 0.01).

3.4. *Between-session reliability of symptoms induction for average outcome*

Intraclass correlation coefficients with 95% confidence intervals (CI), standard error of measurements (SEM) as well as smallest detectable differences of intensity of symptoms (pain, paresthesia) and signal (EDA) are presented in **Table 3**. In general, paresthesia induction was characterized by generally higher reliability when the duration of stimulus was shorter compared to longer duration regardless of the used intensity of stimulation (pressure). The overall agreement between first and second session is demonstrated on **Figure 3**. Averaged data from the first session plotted against data from second session are shown on Bland-Altman plots. In general, negligible bias was found in the agreement for pain (2.54 ± 5.74) and paresthesia (-0.51 ± 3.93), and in case of both symptoms 95% of observations fall within Limits of Agreement (± 1.96 SD of the absolute difference) [4].

3.5. *ICC*

ICCs for paresthesia are characterized by generally higher reliability in the shortest stimuli duration regardless of pressure intensity. Reliability was good ($ICC_{(3,1)}$ = 0.78 - 0.83) for 90 seconds stimuli durations and decreased for longer durations, however, still obtaining moderate reliability ($ICC_{(3,1)}$ = 0.51 - 0.69). Mostly good reliability for pain ($ICC_{(3,1)}$ = 0.75-0.90) was observed in 7 out of 9 stimuli and moderate ($ICC_{(3,1)}$ = 0.70-0.71) in two remained stimuli. ICCs for EDA reached poor ($ICC_{(3,1)}$ = 0.21 – 0.43) to moderate reliability ($ICC_{(3,1)}$ = 0.52 – 0.73) (see **Table 3).**

Table 3. Reliability of pain, paresthesia, and skin conductance

Duration	Intensity	Paresthesia				Pain				EDA			
[s]	[mmHg]	$ICC_{(3,1)}$	95% CI	SEM	SDD	$ICC_{(3,1)}$	95% CI	SEM	SDD	$ICC_{(3,1)}$	95% CI	SEM	SDD
	100	0.78	0.63 - 0.88	2.99	8.29	0.76	0.57 - 0.86	4.89	13.56	0.66	0.14 - 0.86	1.03	2.85
90	150	0.80	0.65 - 0.89	3.58	9.92	0.90	0.81 - 0.95	4.41	12.22	0.52	0.19 - 0.74	1.40	3.87
	200	0.83	0.70 - 0.91	4.19	11.63	0.78	0.61 - 0.88	9.77	27.07	0.73	0.34 - 0.88	1.11	3.06
	100	0.66	0.45 - 0.81	5.6	15.53	0.70	0.49 - 0.83	5.38	14.92	0.61	0.20 - 0.82	1.09	3.01
120	150	0.69	0.48 - 0.82	5.21	14.45	0.80	0.65 - 0.89	6.35	17.59	0.59	0.24 - 0.79	1.16	3.21
	200	0.56	0.31 - 0.74	6.9	19.12	0.79	0.63 - 0.88	8.77	24.32	0.26	-0.04 - 0.53	1.79	4.95
	100	0.57	0.32 - 0.75	6.79	18.82	0.71	0.51 - 0.83	6.24	17.30	0.42	0.09 - 0.66	1.50	4.15
150	150	0.52	0.24 - 0.71	9.56	26.51	0.75	0.53 - 0.87	7.28	20.17	0.21	-0.08 - 0.49	1.89	5.23
	200	0.68	0.47 - 0.82	6.43	17.84	0.80	0.66 - 0.89	8.17	22.64	0.30	-0.01 - 0.57	1.83	5.07

Legend: Note: Intraclass correlation coefficients (ICC, model 3,1) are presented with standard error of the measurement (SEM) and smallest detectable difference (SDD). Reliability is presented for three measured outcomes: pain intensity (Computerized Visual Analogue Scale, CoVAS), paresthesia intensity (CoVAS), electrodermal activity (EDA, physiological signal expressed in mS).

Table 4. Results of correlations between CoVAS (real - time measurement) and overall ratings for paresthesia and pain

		Paresthesia				Pain			
Duration	Intensity	First Session		Second Session		First Session		Second Session	
[s]	[mmHg]	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
	100	0.68	***	0.76	***	0.80	***	0.81	***
90	150	0.76	***	0.71	***	0.80	***	0.75	***
	200	0.47	**	0.65	***	0.82	***	0.86	***
	100	0.77	***	0.84	***	0.82	***	0.75	***
120	150	0.56	***	0.75	***	0.81	***	0.89	***
	200	0.45	**	0.68	***	0.79	***	0.88	***
	100	0.68	***	0.85	***	0.65	***	0.79	***
150	150	0.66	***	0.73	***	0.78	***	0.76	***
	200	0.63	***	0.72	***	0.83	***	0.88	***

Legend: r – Pearson correlation coefficient, *** p < 0.001, ** p < 0.01.

Similar analyses were performed based on AUC and comparable ICC values were obtained (see **Appendix**).

3.6. *Relationship between real-time vs. overall ratings*

Validity analyses revealed a significant correlation between real-time CoVAS ratings and (single) overall ratings collected after each trial by using a traditional VAS scale (**Table 4**). In general, agreement between the two methods to assess symptoms was acceptable for paresthesia with all observations falling within 95% LoAs as indicated by Bland-Altman analysis (**Figure 3**). However, for both symptoms, bias was observed as indicated by shift in mean differences between two methods: overall ratings were higher than real-time for pain (diff. 6.03 ± 6.19) and paresthesia (diff. 16.70 ± 9.68). Pearson correlations between the arm circumference and intensity ratings (pain and paresthesia) were not significant (paresthesia r = -0.09, p=0.56; pain r = -0.04, p=0.82; EDA r = -0.20, p=0.21).

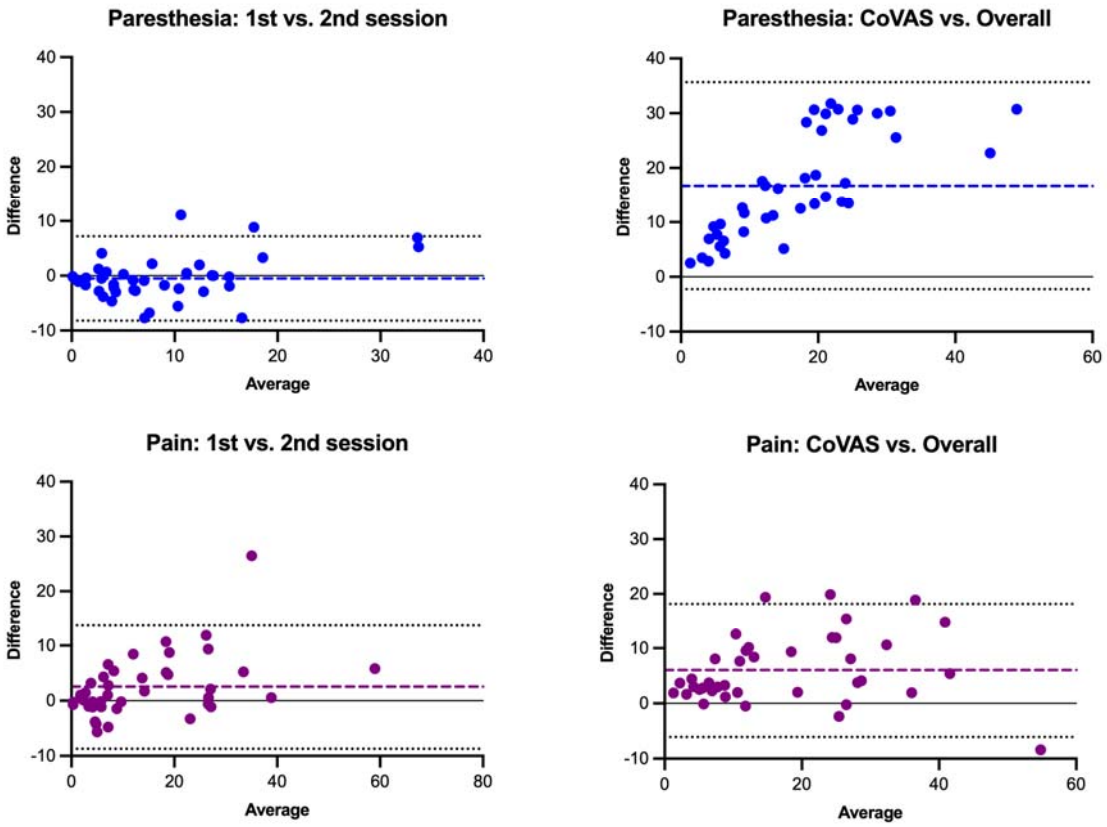

Figure 3. Bland-Altman plots. Agreement between first and second session is shown on the left and agreement between real-time and overall ratings on the right. Bland-Altman plots demonstrate individual differences (dots) between two ratings (first vs. second session on the left, or overall, vs. CoVAS on the right) plotted against average of ratings from two measures (methods). The thick horizontal line (paresthesia in blue, pain in purple) illustrates the mean difference (bias) with its 95% limits of agreement (dotted line). The black horizontal line (zero) indicates absolute agreement.

4. DISCUSSION

In this experiment, the effects of duration and intensity of noxious pressure stimuli on pain and paresthesia in healthy individuals were assessed systematically, using computer-controlled cuff algometry. Interestingly, apart from the stimulus-response relationship between the intensity/duration of the stimulus and the magnitude of sensations, our results showed differential effects of intensity and duration on paresthesia and pain, respectively. Namely, pain tended to increase exponentially with pressure, whereas paresthesia did not. Conversely, the duration of exposure strongly shaped paresthesia but had a lesser effect on reported pain, which remained relatively stable over time. In general, reported symptoms were characterized by a good reliability level, in contrast to EDA data, which was found to have poor reliability as well as no responsiveness to the applied class of stimulation. Divergent trajectories of pain and paresthesia development as well as divergent psychophysical effects confirm that applied stimulation induced different symptoms in a feasible and reliable manner.

Neuropathic pain and paresthesia are often the result of damage or dysfunction within the nervous system. The mechanisms underlying these conditions are complex and multifaceted, involving both peripheral (ion channel modulation, inflammatory mediators etc.) [25] and central components of the nervous system (enhanced synaptic transmission, neuroplastic changes, loss of inhibitory control) [42]. Also hypoxia and oxidative stress play significant roles in exacerbating NP and paresthesia [47]. Hypoxic conditions lead to the release of pro-inflammatory cytokines and other mediators that sensitize nociceptors and contribute to pain and paresthesia. Hypoxia-induced oxidative stress results in the generation of reactive oxygen species (ROS), which can damage cellular structures and enhance pain signaling [47]. In the current investigation, all tissues under the cuff, including skin, muscle, fascia, periosteum and nerves were compressed, activating mechanoreceptors, which resulted in pain [37] as well as paresthesia, arising from reduction of oxygen and nutrient delivery due to prolonged compression and the resulting ischemia [44].

The results of the current experiment showed that paresthesia sensation depends mainly on the duration of the compression and not the intensity of the stimulus (amount of pressure). According to Mogyoros et al. [31], paresthesia occurring during prolonged ischemia is associated with increased axonal excitability that begins within 30 seconds and usually reaches a plateau within 3-5 minutes. In our study, ischemic stimuli lasted 90, 120 and 150 seconds, therefore, they were still within the time of increasing excitation. At the same time, each of the applied stimuli were sufficient to induce ischemia and mimic the variable environment typical for NP. However, the intensity of paresthesia was clearly saturated, hence the additional step from 150 to 200mmHg did not further increase symptoms, thereby confirming a nonlinear stimulus-response relationship. This observation is novel and striking as it may have clinical value, suggesting that more advanced nociception does not necessarily result in more severe paresthesia.

A divergent pattern of results was found for pain perception: Pain increased exponentially when higher pressure was applied. This is in line with several studies that used this experimental pain model and in accordance with stimulus-response characteristics between pain and mechanical [13], electrical [11], thermal [1] stimuli. In a study by Polianskis et al. [38] a significant correlation ($r_s = 0.7$) between pain and applied pressure to the calf muscles was found. Interestingly, pain intensity was not dependent on the duration of the stimulus as was the case for paresthesia. This observation is in line with a later study of Polianskis et. al [40], in which pain was assessed over the course of 10 minutes compression using individualized pain intensities. In the lower pain intensity condition, pain remained stable for approximately two minutes after the initial increase before decreasing slightly. For moderate and more severe pain, the authors observed a clear pattern of adaptation after a mean duration of ~140 seconds. Although further research must confirm this, it is likely that this sudden adaptation could be related to an interaction between pain and paresthesia that reached its peak after 150 seconds.

Given that pain and paresthesia often occur simultaneously in clinical settings, an experimental model was created that would allow for the induction and assessment of both symptoms at the same time. The method based on computer-controlled cuff algometry was used in this experiment for several reasons. Firstly, it is a frequently used technique to induce pain [8,12,13,19,23,27,38], characterized by good reliability [13,26], a finding also confirmed in the present study (ICC = 0.7 to 0.9). Secondly, compared to handheld algometry, computer - controlled cuff algometry allows to apply suprathreshold stimulation of different temporal and intensity characteristics [17,18]. This is important to induce not only pain but also paresthesia that requires a prolonged restriction of oxygen supply [44]. Therefore, the tonic compression seemed to be the most suitable for this study. Additionally, this technique enables real-time monitoring of changes in sensations during stimulation using CoVAS, which was essential for the current experiment [13,38]. Real-time monitoring offers several significant advantages in the assessment of NP and paresthesia. By providing continuous, immediate feedback on sensory changes, this approach enhances both the accuracy and relevance of the data collected.

Real-time assessment captures dynamic changes in pain and paresthesia as they occur, offering a more precise measurement compared to retrospective self-reports. This reduces recall bias and ensures that transient symptoms are accurately recorded [43]. In fact, although we found a significant correlation between overall ratings of pain and CoVAS ratings, the former results in higher ratings than real-time measured ratings via CoVAS with larger discrepancy related to paresthesia. This may be explained by the trajectory of paresthesia's development which was gradual whereas pain was more stable and thus, the overall ratings of pain -based on recall- seemed to be less cognitively demanded that ratings of paresthesia. Furthermore, a "peak-end" artifact could be more likely present in

paresthesia than in pain. In this artifact people tend to provide single rating of symptoms shaped by the “peak” of the experienced pain and how the stimulus inducing sensation ended [20].

Surprisingly, no effect of stimulus parameters was found in EDA nor any correlation with EDA signal was found between paresthesia and pain. However, the literature in pain is not clear in this regard, with some studies showing a relationship with pain and some don’t. In one study, authors argued that EDA can encode the intensity of a stimulus rather than the intensity of pain [33], whereas others found that EDA responses can discriminate between different levels of pain appraisal [6,30]. However, in a study by Breimhorst et al. [6], phasic stimulation was used instead of tonic stimulation which can explain different results. Of note, the current EDA measurement was done at the same side (hand) which was exposed to nociceptive stimulation. Given the nature of the stimulation, it is likely that prolongated compression of the limb could have also impaired transduction within sympathetic nerve nerves, which could introduce another source of variability of the EDA signal. Notwithstanding, possibility exists that a lack of EDA responsiveness is due to the potential floor effects as the reported pain was in the current study relatively low. In the study by Mischkowski et al. [30], the EDA exerted more response when the stimulus was perceived as painful as opposed to when it was judged not to be painful. This limitation, was however, unavoidable and determined by the highest stimulus of 250 mmHg applied by 150 seconds. This maximal stimulus intensity was necessary to ensure safety and tolerance of the stimulation by most participants. Further research should focus on EDA in the context of limb ischemia and symptoms induced by a different set of stimulation as the literature in this field is scarce.

The findings of this study have several important implications for both clinical practice and experimental pain research, particularly in the context of NP conditions. The ability to measure pain and paresthesia simultaneously through computer-based cuff algometry provides a more nuanced understanding of these symptoms and their interrelationship, which can significantly enhance diagnostic and therapeutic approaches. Neuropathic pain is notoriously complex, often presenting with co-occurring symptoms such as pain and paresthesia. Traditional pain models tend to focus on a single symptom, thereby missing the intricate interplay between various neuropathic symptoms. By demonstrating that pain and paresthesia can be reliably induced and measured simultaneously, this study offers a more comprehensive surrogate model for studying pain with neuropathic component. This dual-symptom approach allows researchers to i) dissect mechanistic pathways: understanding how different stimuli affect pain and paresthesia can elucidate the distinct and overlapping neural mechanisms involved in NP, ii) characterize symptom interactions: by capturing the temporal dynamics and intensity-response relationships of both symptoms, researchers can better understand how these symptoms influence each other and contribute to the overall pain experience. The ability to measure both, pain and paresthesia, in a controlled setting may also have significant

implications for clinical practice. Clinicians can use this method to monitor treatment efficacy more precisely. For instance, evaluating how interventions affect both pain and paresthesia can provide a more holistic measure of therapeutic success, beyond just pain reduction.

5. ACKNOWLEGDEMENTS

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