A Preliminary Study on Electrocardiogram Response During Pain Induction

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Abstract. Pain is a complex phenomenon that arises from the interaction of multiple neuroanatomic and neurochemical systems with several cognitive and affective processes. Nowadays, the assessment of pain intensity still relies on the use of self-reports. However, recent research has shown a connection between the perception of pain and exacerbated stress response on the Autonomic Nervous System (ANS). The ANS, which is divided into the Parasympathetic Nervous System (PNS) and the Sympathetic Nervous System (SNS), functions as the subconscious regulator of the body. As a result, there has been increasing analysis of the autonomic reactivity with the objective to assess pain. The goal of this study was to explore and understand different responses in the electrocardiogram (ECG) signal when in the experience of pain. For this study, ECG was simultaneously recorded while a pain-inducing protocol (Cold Pressor Task - CPT) was implemented. Several features were extracted from the ECG to analyse differences related to pain induction tasks. The results obtained showed a statistically significant increase in the heart rate during the painful periods in comparison with non-painful periods. Additionally, heart rate variability features demonstrated a decrease in the PNS influence. These results are a step further in understanding the ECG response during the experience of pain, supporting the awareness and insights over physiological interactions within the pain experience.

Keywords: ANS · CPT · ECG · Pain induction · Feature extraction · Pain assessment

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1 Introduction

Pain is a complex biopsychosocial phenomenon caused by damage or potential damage in the tissues and serves a vital protective function. The International Association for the Study of Pain revised the definition of pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [1]. Pain is a common symptom in almost every clinical practice. This is particularly true in neurological and musculoskeletal problems [5].

The presence of pain and, moreover, its intensity, influences a physician's clinical judgement, the selection of treatments and therapeutics, the potential surgical indications, and the subsequent prognosis. An accurate assessment is a critical factor, affecting decision making in patient management, treatment, and outcomes. As of today, pain assessment still relies primarily on self-report, both in clinical and experimental settings. Self-reports are generally easy to obtain, require practically little to no equipment, allow for comprehensive information collection, and exhibit typically good reliability [5]. Nonetheless, circumstances exist where this is not possible or where it is unreliable [2]. In these situations, surrogate markers utilise changes in behavioural or psychological parameters. However, their use may be inaccurate, hampered by observational bias, or influenced by disease processes or pharmacological interventions [6]. Thus, objective approaches to measuring pain experience would provide an important complement to self-reports [2]. Although the study of how physiological indicators correlate to pain is still at an early stage, it has become a promising research area. Consequently, the main goal of this study aims to explore and describe ANS reactions related to pain and identify relevant features from physiological signals associated with it.

This work is organized as follows. The next Sect., 2, presents related works on exploring physiological reactions, namely through ECG, in the experience of pain. Section 3 presents the data collection and methodology for data analysis, while Sect. 4 presents the obtained results. Finally, the results are discussed in Sect. 5 prior to presenting the conclusions of our study in Sect. 6.

2 Related Works

Pain is thought to exacerbate the autonomic response to stress, a rationale supported by evidence showing a neuroanatomical overlap between nociceptive and autonomic pathways [2]. For example, studies have shown that the application of pain stimuli induces significant heart rate acceleration. Therefore, there has been a growing interest in the use of autonomic reactivity as an objective marker of pain [3–5].

Loggia et al. [5] studied the alterations in the Heart Rate (HR), skin conductance, and pain ratings in response to heat stimulus of different intensities, which range from warm to pain-inducing. The data was analysed from two different perspectives: the correlation between the autonomic response and pain intensity

in subjects separately (subject analysis) and the correlation between the average pain intensity and the autonomic responses to the same temperature in all individuals (group analysis). The results demonstrated that an increase in pain intensity generated an increase in both HR and skin conductance. The subject analysis revealed a higher correlation with skin conductance, leading to a belief that this metric is more sensitive to changes in perception. However, the magnitude increases of the skin conductance did not significantly correlate with the magnitude of pain intensity, suggesting that this measure alone does not predict the absolute level of pain reported by the subject. The opposite was true for HR, as it did not reliably predict verbal responses to pain on a subject basis but did on the group level. These differences suggest that, although HR is affected by pain perception, it is a very noisy measure.

The Cold Pressor Task (CPT) is a pain-inducing method that requires individuals to immerse one hand (or forearm) in cold water for as long as they can tolerate or during a fixed period of time. The main advantages of this method rely on its portability, minimal training to use, and few risks. The primary disadvantage of the CPT is the significant methodological divergences in its implementation and in the measurement of pain outcomes, crippling the comparison of results from different studies [3,4,8,9]. There is increasing information linking the feeling of pain with the ANS. Therefore, several studies have investigated and recorded the alterations of the ANS with the use of the CPT.

One such case was the work of Hampf [3], who planned to quantify the changes in skin impedance, HR, and facial skin temperature when healthy volunteers were subjected to acute pain through a CPT (with water at 0 °C). A total of nineteen participants were included in the study. The results showed an increase in all the parameters calculated during the CPT, in comparison to those calculated during the baseline. However, only the skin conductance increase was statistically significant.

Kregel. et al. [4] analysed the relation between efferent sympathetic nervous system activity to skeletal muscle (MNSA) and pain sensation during localised skin cooling. Ten subjects took part in the study, immersing their hand in different temperature water baths for three minutes each. The levels of temperature in the bath range from warm non-pain inducing to mid-level (14 °C) to cold (7 °C and 0 °C - pain-inducing). The participants went in order from the warmest to coldest temperature, with a ten-minute interval between the recovery three-minute period of the last water tank and the three-minute baseline of the next. While the study was being performed, the MNSA, BP (blood pressure), HR, and breathing were continuously recorded. The observations of this study demonstrated that there was no evident influence on MNSA when the participants were subjected to non-painful skin cooling. During the hand immersion in ice water, there was a progressive rise in MSNA as skin temperature started to decrease. Regarding HR, there was a significant rise during the initial phase of the 0 °C, which was expected. Even so, the HR consistently increased in less painful water temperatures, although on a smaller scale. As for the BP, it showed no changes [4].

3 Materials and Methods

This section describes the protocol for data collection and presents the methods applied for analysing the ECG response during the induction of pain through cold pain stimuli implemented as a CPT. The different methods used to analyse the data were implemented in Matlab R2021a (MATLAB R2021a & Simulink R2021a) [7]. As the proposed work focuses on the ECG response in the experience of pain, it will be only presented the protocol for ECG data collection.

3.1 Data Collection

Aiming to study the physiological changes that pain provokes, 45 participants were subjected to a pain-inducing protocol (CPT), while the ECG signal was being collected. This study was approved by the Ethics and Deontological Council of the University of Aveiro (number 09-CED/2019).

All the participants were recruited from the local community, they were healthy, did not suffer from any disease that causes chronic pain, did not present any mental illness or neurological disorder, and, lastly, could comprehend and answer to self-report measures. As explained before, we studied a total of 45 participants, 27 male and 17 female, with ages between 21 and 59, with an average age and standard deviation of 33 and 11 years old, respectively.

To perform the CPT, two specially designed tanks were used. These were produced to be able to sustain the water at the desired temperature. The physiological data were collected with the Biosignalsplux® Explorer tool kit, with a sampling frequency of 1000 Hz. The ECG was collected with a triode configuration: two electrodes were placed on the right and left side of the participant's ribcage, and a reference electrode was placed above the pelvic bone. Additionally, to mark the different epochs, a handheld switch directly connected to the hub was used.

After obtaining the participant's informed consent, and before starting the procedure, the participants had to respond to the instrument for data collection regarding their age, gender, and health status, thus ensuring that they complied with the inclusion criteria. That same data collection sheet was later used to fill out their pain level. The participants were asked which hand was their non-dominant and seated accordingly. All the participants were facing a wall during the study, to ensure as few distractions as possible. The protocol started with a five-minute baseline recording, where the participant had to be seated, at a comfortable position, with their arm close to their body, trying to avoid movements. After, they were asked to immerse their hand and forearm inside the warm water tank for two minutes, to ensure that all the participants started the CPT with similar skin temperatures (37 °C). Before the end of this task, the level of pain, with a numerical rating scale (NRS), was assessed. Afterwards, for the induction of pain, the participants immersed the arm into the cold-water tank and the CPT started. If the participant was unable to withstand the CPT for the whole two minutes, they could withdraw their hand from the cold tank. In this case, the participant was advised to notify their wish to remove the arm from the

tank and, before doing so, to report their current pain level and the level of the maximum pain experienced during the CPT. If the participant was able to withstand the entire CPT, the current and maximum pain levels were reported at the two-minute mark. Right after removing the arm, they again reported their pain level and the BP was measured. The participant transferred the arm to the warm water tank for two minutes of immersion. Next, the hand and forearm were dried, and, while seated in a comfortable position, a five-minute rest period, similar to the initial baseline, commenced. At the three-minute point during this rest period (around five minutes after the end of the CPT), they were asked to give their current pain level and to report the maximum level of pain they felt in retrospect.

3.2 Data Analysis

After data acquisition, the raw ECG was filtered considering the frequencies between 0.5 Hz and 40 Hz. After, the ECG data was normalized according to the baseline epoch, which corresponds to the first five minutes of this study. The feature extraction was done using the Neurokit2[1] in Python. After the data was processed, it was divided into epochs according to the pressing of the triggers. The five epochs created are the five-minute baseline recording (Baseline), the first two-minute recordings of the hand and arm in the warm water tank (WarmWater1), the CPT recording, the two minute recordings of the warm water tank for the second time (WarmWater2) and, finally, the last five minute rest (Rest). Afterwards, all features were subjected to statistical analysis, in which the significance level (α) was set at 0.05, to investigate differences in the extracted features in the several epochs. As all of the features failed to be normally distributed, the differences between the five different epochs were evaluated with the non-parametric Friedmann. When a significant difference was found between the five epochs, the Wilcoxon signed-rank test, with Bonferroni correction, was performed to evaluate which epochs were significantly different from each other. The statistical analysis was done using scikit posthocs [11]. This python package provides posthoc tests for pairwise multiple comparisons. Scikit posthocs package is dependable on the statsmodels module, in which the multiple test is responsible for adjusting the p values to minimize type I and type II errors [12]. The results were then plotted on a heatmap to facilitate their interpretation.

4 Results

Six of the 45 original volunteers had to be taken out of the study. As such, a total of 39 individuals were used in this study.

Regarding ECG features, the HR was computed and the maximum and minimum values of each ECG cycle were calculated, R peaks and S peaks, respectively. Afterwards, for each epoch, the averages of those were computed.

[1] https://neurokit2.readthedocs.io/en/latest/.

Table 1. Description of the extracted ECG features.

Feature	Description
Mean HR	Number of beats per minute (mean)
R peaks	Maximum value of the ECG cycles (upward deflections)
S peaks	Minimum value of the ECG cycles (downward deflections)
RMSSD	Root mean square of successive differences between normal heartbeats. It is a reflection of the beat-to-beat difference in the HR and is used to estimate the alteration of the HRV caused by the vagus nerve
pNN50	Percentage of successive RR intervals that are greater than 50 ms. Firmly correlated with the PNS activity
SampEn	Measures the regularity and complexity of a given signal. Smaller values indicate a regular and predictable signal

With respect to the HRV features, and due to the different lengths of the epochs and the short term of the CPT epoch, only the following features were considered: RMSSD, pNN50 (time-domain features), and SampEn (non-linear feature). The description of the used features is presented in Table 1.

Figure 1, represents the results for the normalised mean HR. It is clear that the most prominent boxplot is the CPT, being the epoch with the higher HR values, showing a response to the stress caused by the pain. Observing the matrix statistical results, there is a statistically significant difference between the mean HR during the CPT and from the remaining epochs.

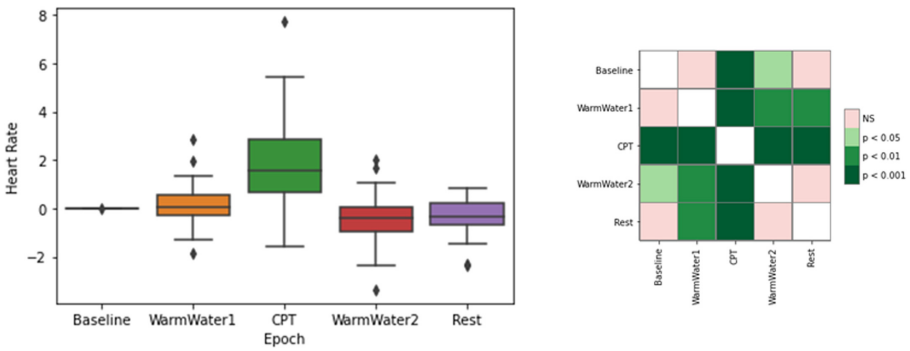


Fig. 1. Boxplot of mean HR values for each epoch (left) and respective p-values between different epochs, with Bonferroni correction (right).

Figure 2 regards the maximum value of the ECG cycles, which correspond to the R-peaks, showing a median value increase for the normalised R-peak amplitude from the Baseline to the WarmWater1, with little variation of the

dispersion. This increase is about 7.7% from the Baseline (4.04 mV) to the WarmWater1 (4.35 mV). However, this is followed by a decrease of 2.55% during the CPT (4.24 mV). The median, rises, once again, reaching its peak with an increase of about 6% during the WarmWater2. The amplitude returns to near its original value (4.11 mV) during the Rest period. Although slight, there seems to be a reaction when the participants placed their hand on the water. However, there is no significant difference between the non-pain inducing and pain-inducing water temperatures on the maximum amplitude of the ECG cycles. The statistical analysis corroborates this, as it did not show any inter-epochs significant differences, with exception of the WarmWater2 for the Baseline and the Rest, the epochs with the highest and lowest amplitude values, respectively. These results suggest that the maximum ECG amplitude is not a suitable feature to examine the presence of pain in an individual when subjected to the CPT.

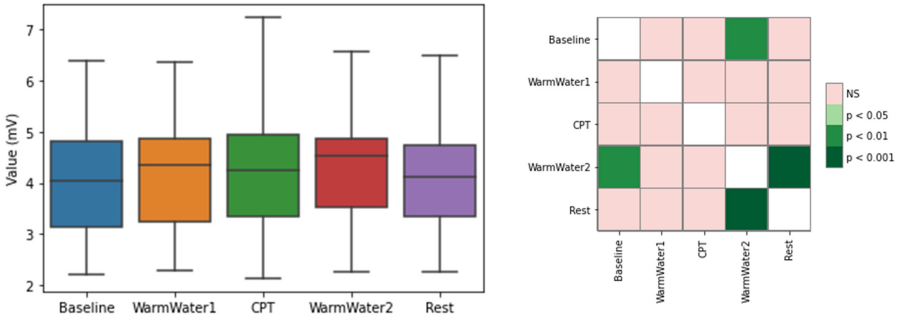


Fig. 2. Boxplot for the mean maximum ECG cycle values (left) and respective matrix of calculated p-values between different epochs, with Bonferroni correction, for the (right).

Another ECG-feature studied was the minimum value of the ECG cycles, which corresponds to the S-peak. Figure 3 shows a decrease of the median value from the Baseline to the WarmWater1, followed by a decrease from this epoch to the CPT. After the pain-inducing procedure, the minimum amplitude of the ECG cycles gradually increased. The statistical analysis for this feature shows that the CPT had significant differences from all the other epochs, being statistically more significant with the Baseline and Rest periods. There were no significant differences between the Baseline and Rest. Finally, regarding the WarmWater1 and WarmWater2, there was, also, no significant difference between them. Nevertheless, both had statistically significant differences from the other groups.

Figure 4 shows the RMSSD results. Looking at the graph, the epoch with the lowest values is the CPT. As for the other epochs, the RMSSD values are higher. However, the Baseline and, especially, the WarmWater1 appear, in general, to have slightly lower levels when compared to the Rest and WarmWater2 epochs. Finally, analysing the p-values obtained by the Wilcoxon test, there is only a

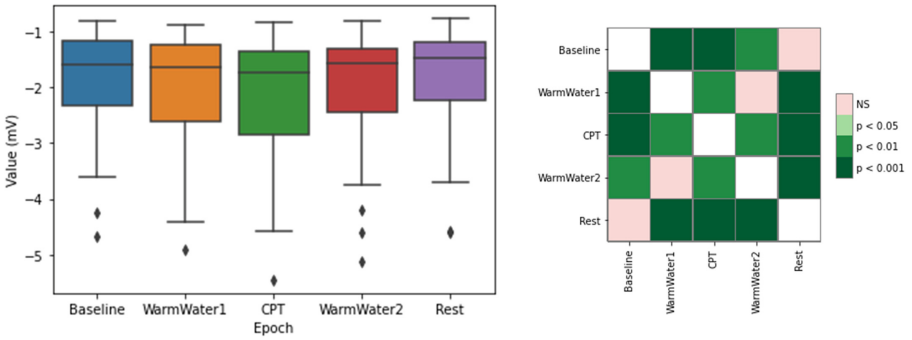


Fig. 3. Boxplot for the mean minimum ECG cycles (left) and respective matrix of calculated p-values between different epochs, with Bonferroni correction, for the (right).

significant difference between the CPT and the WarmWater1 and between the CPT and the following epochs.

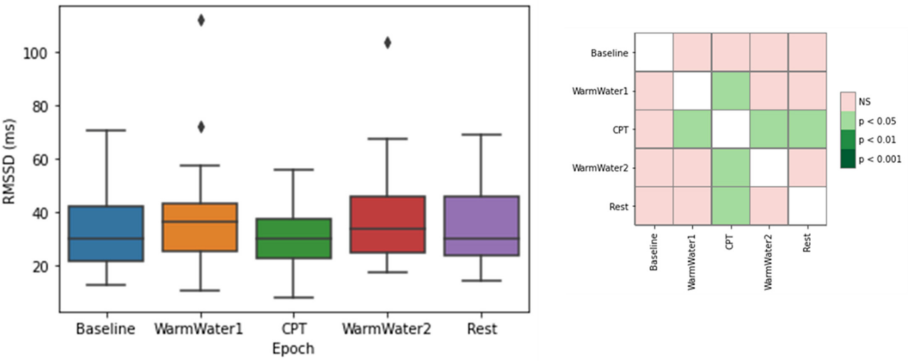


Fig. 4. Boxplot of RMSSD values for each epoch (left) and respective p-values between different epochs, with Bonferroni correction (right).

Figure 5 displays the pNN50 results. In accordance with the findings of the RMSSD, the epoch with the lowest pNN50 values was the CPT. In this epoch, the participant with the highest pNN50 had less than 40% of their heartbeats longer than 50 ms. Overall, the median values in each epoch seem to be similar. Even so, the epoch with the lowest median was the CPT (7.7%), with a 0.9% difference when compared to the Baseline and 2.4% compared with the WarmWater1 and Rest, while the WarmWater2 was the epoch with the highest median pNN50 (11.4%). There seems to be a consistent positive skewness on the boxplots, which means that the values of the upper quartile are more dispersed. This may be due to natural differences between the participants. Along with the protocol, there is a general increase of values from the Baseline to the WarmWater1, followed by a decrease during the CPT and a subsequent rise during the WarmWater2 and

Rest epochs, indicating a recovery after the CPT. Unlike the previous features, there was no significant statistical difference shown between the epochs.

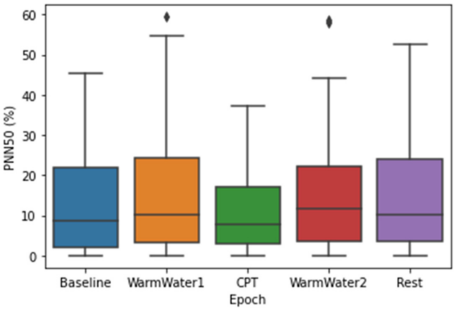


Fig. 5. Boxplot of pNN50 values for each epoch.

Finally, the regularity and complexity of each epoch are presented in Fig. 6, through the SampEn values. The epoch with the lowest value was the CPT. Another interesting observation is the results in the WarmWater2, which had generally higher values and a noticeable increase in the median value, which implies less predictability. Looking at the Baseline and WarmWater1, both have equal median values (1.45). However, the values showed greater dispersion on the latter, which denotes greater behavioural differences in participants when compared to the former epoch. Lastly, the Rest epoch had a similar mean value to the two initial epochs and smaller dispersion, suggesting that, overall, the participants were able to recover after the CPT. The statistical analysis (Fig. 6-right) only indicates a statistically significant difference between the CPT and the remaining epochs, with the exception of the Rest.

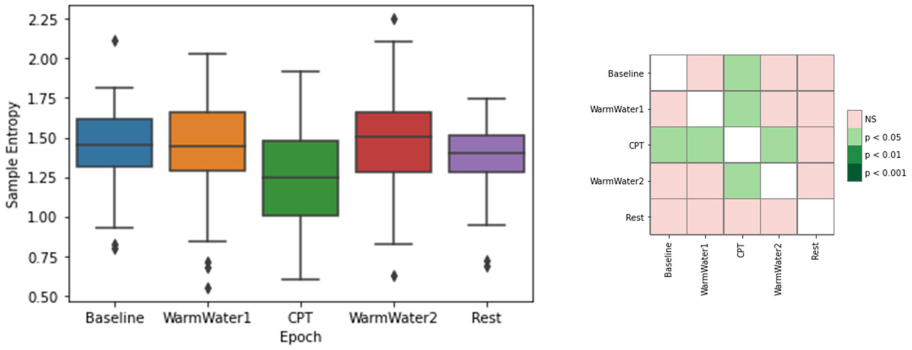


Fig. 6. Boxplot of SampEn values for each epoch (left) and respective p-values between different epochs, with Bonferroni correction (right).

5 Discussion

For the study of induced pain, the features extracted from the ECG seemed to respond in accordance with what was hypothesized. The results on the meanHR, were similar to what was described in previous literature [2,3,5,10], and is most likely a result of the increased sympathetic outflow on the body. The Wilcoxon results also showed significant differences between epochs. As for the RMSSD, a HRV metric which is an estimation of the vagally mediated changes, demonstrated a decrease in the parasympathetic outflow to the cardiovascular system during the pain inducing task. The RMSSD also showed lower values for the two epochs before the CPT, when compared to those that preceded it. This may be a result of a higher level of anxiety felt by the participants before being subjected to pain. The statistical analysis also corroborates this conjecture, as there were no significant differences observed between the Baseline and CPT. The SampEn, which measures the regularity of the signal, demonstrated that the pain induced by the CPT caused a reaction in the participants that lead to a more consistent heartbeat pattern in their cardiac system. As described above, the WarmWater2 had higher values. This implies less predictability and may be attributed to the recovery time that the body needed to return to the initial state by decreasing its HR. Lastly, the mean amplitude of S-peaks showed a progressive decrease in values until the CPT, followed by a progressive increase in the latter epochs. The statistical analysis for this feature also endorsed that there was a response in the S-waves of the ECG to the pain. In general, the results for the ECG features show that the cardiac system seems to react to the cold-painful stimulus.

6 Conclusions

Overall, the results of this induced pain study are quite similar to what was discovered in previous related works. With the exception of the pNN50 and the R-peaks, the statistical analysis showed that the remaining features are suitable to be used to identify the experience of pain. This opens the possibility for derive more accurate metrics to evaluate pain rather than self-reports.

Nonetheless, since the collected dataset has other physiological signals, efforts should be endeavoured to develop a multi-perspective on the induced pain.

A substantial setback of the used dataset is the short length of time recordings of the CTP, which hindered the study of the majority of HRV metrics and did not permit the investigation of the influence of the SNS on the cardiovascular system. As such, increasing the length of the CPT should be considered in future works.

Another hindrance to this study was the low number of participants, which limited the research scope. The study would also benefit from a larger group of individuals, allowing additional gender or aged based studies to find group-based differences.

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