Sensor-Based Measurement of Nociceptive Pain: An Exploratory Study with Healthy Subjects

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Abstract. Valid assessment of pain is essential in daily clinical practice to enhance the quality of care for the patients and to avoid the risk of addiction to strong analgesics. The aim of this paper is to find a method for objective and quantitative evaluation of pain using multiple physiological markers. Data was obtained from healthy volunteers exposed to thermal and ischemic stimuli. Twelve subjects were recruited and their physiological data including skin conductance, heart rate, and skin temperature were collected via a wrist-worn sensor together with their self-reported pain on a visual analogue scale (VAS). Statistically significant differences ($p < 0.01$) were found between physiological scores obtained with the wearable sensor before and during the thermal test. Test-retest reliability of sensor-based measures was good during the thermal test with intraclass correlation coefficients ranging from 0.22 to 0.89. These results support the idea that a multi-sensor wearable device can objectively measure physiological reactions in the subjects due to experimentally induced pain, which could be used for daily clinical practice and as an endpoint in clinical studies. Nevertheless, the results indicate a need for further investigation of the method in real-life pain settings.

Keywords: Pain · Sensors · Physiological data · Healthy subjects

1 Introduction

Pain is a common physical sensation, and its perception is highly subjective, based on personal experience [1]. Pain is accompanied by many elements that will modify its expression including fear, anxiety, and depression [2]. The demand for high quality postoperative pain relief has increased partly based on the goal of delivering an efficacious healthcare to reduce lengths of hospital stay and to reduce associated healthcare costs [3]. Therefore, there is a need for valid measurement of pain that can be used in routine clinical practice as primary and secondary endpoints [4] and for enhancing the patients' quality of life by suggesting an individualize treatment plan.

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Opioids such as morphine, oxycodone, and fentanyl, commonly used in postoperative care, act on opioid receptors in the brain. Nevertheless, prolonged use of opioids postoperatively is one of the reasons for both increased opioid use and addiction development in many patients [5]. In today's healthcare, pain treatment occurs initially during the hospitalization phase. However, a large part of pain treatment and rehabilitation occur at home [6]. Where unsupervised use of opioids leads to side effects such are respiratory insufficiency and opioid addiction [7].

Pain is difficult to measure because of its multifaceted and subjective nature. Pain can be either nociceptive or neuropathic. Nociceptive pain is usually acute and is developed in response to external stimuli whereas neuropathic pain refers to damages in the nervous system that are not because of external stimuli. In routine clinical practice, Visual Analogue Scale (VAS) and Numeric Rating Scale (NRS) measure the intensity or frequency of various symptoms related to pain. However, self-rating instruments are highly subjective, based on previous experience of pain [8] and depend on many factors other than pain, e.g. mood [9].

Therefore, it is challenging to measure pain in an objective manner. Moreover, adequate pain control as well as tools to monitor dose consumption of the opioids prescribed at home are lacking. Coupling objective nociceptive pain assessment methods based on physiological indicators with dose monitoring devices enable collection of information that will reduce the risk associated with opioid treatment. It could reduce the prolonged postoperative opioid use and the effect of postoperative exposure to opioids such as misuse among high-risk patients.

The aim of this study was to develop an objective method for nociceptive pain assessment using wearable sensors. The pain-related information expressed as physiological signals was collected from healthy subjects exposed to experimental pain stimuli using sensor devices. We also investigated if multimodal physiological data could be used to identify pain-related and no pain-related episodes.

2 Methods

2.1 Study Subjects

Twelve healthy subjects were recruited in an open, single site exploratory study conducted at the Multidisciplinary Pain Centre at Uppsala University Hospital, Sweden (Table 1). All the research subjects provided, after they have been informed about the study, a written informed consent to participate. The study was approved by the Swedish Ethical Review Authority.

Table 1. Subject characteristics, mean ± standard deviation.

Variable	Value
Gender	8 males, 4 females
Mean age (years)	24.8 ± 6.8
Mean length (cm)	177.8 ± 8.4
Mean weight (kg)	75.2 ± 13.2
Mean BMI	23.6 ± 3.2

2.2 Data Collection

2.2.1 Collection of Physiological Data

To evaluate and induce pain in controlled settings, two human experimental pain models including thermal (cold) stimuli and ischemic pain were employed.

The subjects immersed their non-injured hand up to the wrist in a cold-water bath at 4 °C cooled by a refrigerated water circulator (Somedic, 2015, Sweden), for 2 min. The water level was set at a height of 7 cm to keep the stimulated area consistent. Participants were told that they would be informed by the researcher when this time period had elapsed. They were also told that they could remove their hand from the bath before 2 min if the examination become too painful. Time to withdrawal of the hand (Cold-Pressor Tolerance - CPT, seconds) from the cold water was recorded. The subjects continuously rated the pain intensity during the test stimulation and the conditioning stimulus. Pain intensity was measured using a computerized visual analog scale which ranged from 0 (no pain) to 100 (most intense pain tolerable).

During the Ischemic Block Test (IBT) the subjects were comfortably lying in a reclined position with their neck and head supported and the right forearm resting comfortably on a table in a semi-pronated position, with the elbow slightly flexed. A well-padded tourniquet was applied on the forearm, just below the elbow and inflated to 100 mm Hg above the subject's systolic blood pressure. The tourniquet was inflated for a maximum of 30 min.

Each subject performed both tests and the order of the tests was randomized, using a paper-based, sealed envelope technique. The subjects had a minimum of 45 □ 15 min between the two tests and they were instructed to tolerate the cold or the painful pressure for as long as they possibly could, but that they can terminate the trial at any time.

While performing the tests the patients wore a wrist-worn sensor (Empatica E4) on the other arm to collect physiological data including skin conductance, skin temperature, movement, and heart rate. The Empatica E4 sensor [10] was equipped with a photoplethysmography (PPG) sensor, which collected blood volume pulse used to calculate heart rate variability, a 3-axis accelerometer, which collected acceleration and physical activity, a galvanic skin response (GSR) sensor, which collected electrodermal activity (EDA), and a sensor to measure peripheral skin temperature. The EDA data was extracted by using two electrodes connected to the palm of the subjects. The sampling frequency was fixed at 64 Hz for PPG, 4 Hz for EDA, 4 Hz for temperature, and 32 Hz

for acceleration signal. The data were stored locally and then transferred to a secure cloud service.

2.2.2 Self-assessed Pain

During CPT the VAS pain was collected using an electronic device. During the test the subjects were asked to slide a horizontal bar in the device using their free arm. The VAS pain score ranged from 0 mm (no pain, lower anchor) to 100 mm (unbearable pain, upper anchor). Subjects rated the intensity of cold test-stimulus continuously until they became pain free. The pain scoring during ischemic test continued minimum 3 min after the test or until pain and physiological signals have normalized.

During IBT the pain was reported orally on the NRS scale (0-no pain, 10-maximal pain) every minute during the first 10 min of the test and then every second minute till the 30 min interval. The reporting of pain continued till maximum 15 min after the tourniquet pressure was released and physiological signals have normalized.

2.3 Data Analysis

2.3.1 Feature Extraction

The recorded signals of the sensor were processed to extract clinically relevant information related to pain. The acceleration data were omitted since the subjects were specifically asked to move during the tests. During the thermal stimuli the body temperature might have influenced the results and due to this fact, the peripheral skin temperature signal was omitted when analyzing the data collected during the CPT.

For the IBT test, a window of 3 min was used to extract the features. For the CPT test, the signals were separated into two windows: before the test (baseline) and during the test (intervention). In total, 58 features were calculated: 17 from the EDA of the PPG sensor, 17 from blood volume pulse (BVP) and 12 from heart rate (HR) of the PPG sensor, and 12 features from peripheral skin temperature signal.

For each of the four signals: EDA, BVP, skin temperature, and HR, the following 12 features were calculated: (1) mean of the signal, (2) standard deviation of the signal, (3) skewness of the signal, (4) mean of low-frequency coefficients extracted from first level Discrete Wavelet Transform (DWT), (5) standard deviation of first level low-frequency DWT coefficients, (6) mean of first level high-frequency DWT coefficients, (7) standard deviation of first level high-frequency DWT coefficients, (8) mean of second level high-frequency DWT coefficients, (9) standard deviation of second level high-frequency DWT coefficients, (10) mean of third level high-frequency DWT coefficients, (11) standard deviation of third level low-frequency DWT coefficients, and (12) Approximate Entropy of the signal. Ten additional features were calculated for EDA and BVP based on the study performed by Nabian et al. [11]. For EDA the following additional features were calculated: mean duration of skin conductance response, mean amplitude of skin conductance response, mean rise-time skin conductance response, mean skin conductance, and number of detected skin conductance responses. For BVP, mean diastolic pressure, mean systolic pressure, mean dicrotic peak pressure, mean dicrotic notch pressure, and mean arterial pressure were calculated and used in the feature set.

To reduce the dimensions of the 58 extracted features from the different modalities a Principal Component Analysis (PCA) was applied. After PCA, the first 4 principal components (PCs) were used in subsequent analysis. All the feature extraction analysis were performed with MATLAB 9.6.

2.3.2 Statistical Analysis

All statistical analysis was performed with Minitab 19. Descriptive statistics are presented as means and standard deviations for continuous variables and absolute numbers and percentages for categorical variables. To assess if the PCs (principal components) were coherent with subjective, perceived pain, VAS correlation coefficients were calculated. To assess differences in mean PCs between the baseline (no stimuli) and intervention periods one-way ANOVA was applied. Test-retest reliability of the PCs was assessed by calculating their intraclass correlation coefficients (ICC) between the baseline (before applying tourniquet pressure) and the first window that is the first 3 min of the IBT test.

3 Results

3.1 Self-assessed Pain

For the IBT, the mean NRS increased from the first 3 min window till the end of the test (Fig. 1) and was significantly different ($p < 0.05$). For the CPT test, the mean VAS was significantly different ($p = 0$) between the baseline and intervention windows (Fig. 2).

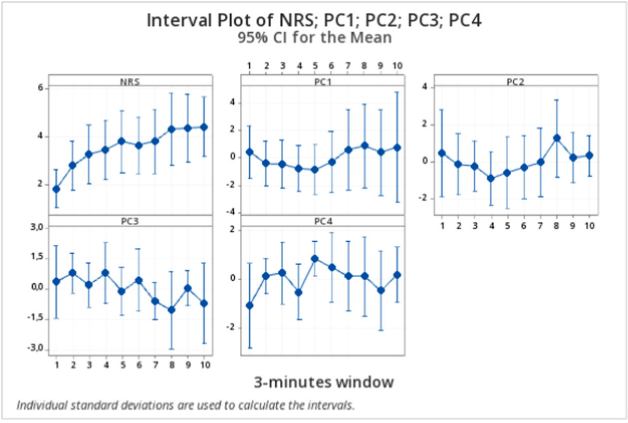

Fig. 1. Mean NRS and PC1–PC4 per 3 min window during the ischemic block test.

3.2 Sensor-Based Measures of Pain

For the CPT test, only mean PC3 was significantly different between the baseline and intervention windows ($p < 0.01$, Fig. 2).

For the IBT test, there were weak correlations between NRS and the four PCs with correlation coefficients ranging from 0.067 to 0.217. After comparing the NRS and PC scores between the baseline window (3 min before the IBT test) and the last window (last 3 min before tourniquet pressure release) it was shown that the duration of tourniquet application corresponds with increased pain scores, demonstrated by significant differences NRS pain ($p = 0$) and PC4 ($p < 0.005$) (Fig. 1). All four PCs, except PC2, demonstrated good test-retest reliability (Table 2).

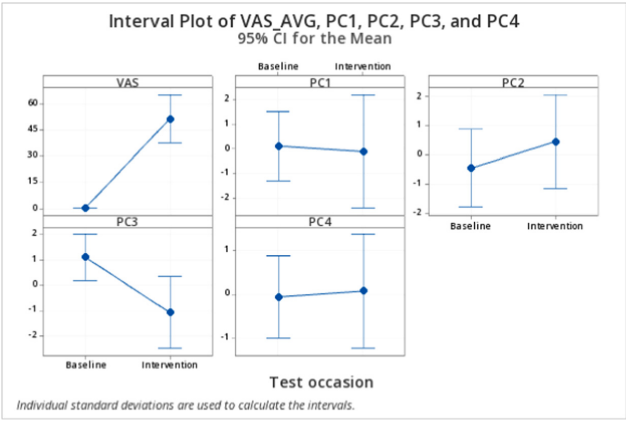

Fig. 2. Mean VAS and PC1–PC4 during the baseline and intervention test occasions during the cold pressor test.

Table 2. Intra-class correlation coefficients of VAS and PC1–PC4 between the baseline and follow-up test windows during the ischemic block test.

Variable	ICC
VAS	1
PC1	0.84
PC2	0.22
PC3	0.89
PC4	0.8

4 Discussion and Conclusion

In this study a multimodal sensor-based method for quantification of experimental, nociceptive pain intensity induced by two pain stimuli models (thermal CPT and ischemic IBT tests) is proposed. The method used information related to pain collected from multiple sensors (temperature, PPG, and GSR). The data were obtained from healthy subjects exposed to experimental pain stimuli of different intensities and durations.

A weak correlation between the PCs and self-assessments of pain using VAS and NRS was found. Correlating objective measures of pain to self-assessed pain remains controversial [12]. When no correlation is found the assumption is that the objective method is not valid. On the other hand, when good correlation is demonstrated the objective method does not add any value in the assessment of nociceptive pain, which could indicate that the easy-to-use pain rating scales could be preferred in daily clinical practice. As suggested by Wagemakers et al. [12] an additional measure to validity is test-retest reliability to assess the reproducibility of the sensor-based scores. From Table 2, the PCs, except PC2, had good test-retest reliability indicating that the scores show consistent values associated with the healthy subjects.

The results indicated that the mean PC3 was significantly different between the baseline and intervention windows of the CPT test (Fig. 2). The PCs were not derived by mapping them to self-assessed pain scores but instead they were obtained in a data-driven manner by fusing information from multiple sensors through reduction of individual features in a new data space using PCA, which can be seen as strength of the proposed methodology. The findings from this study suggested that the proposed method of collecting data from multiple devices could be used to detect and differentiate episodes of experimental-induced pain from periods with no pain. This could lead to a low-cost method to determine and quantify a patient's pain more objectively. Similar results were obtained by Chu et al. [13] using a multiple physiological signal method. Their method was developed in healthy volunteers subjected to an externally induced pain by an electrical simulator. The method could correctly classify pain intensity during different electrical stimulus levels.

The results from this study indicate that combining multiple physiological markers can be used to objectively measure pain, which is complex in nature. This multimodal approach seems to provide a good prediction of pain intensity [14]. In the study it can be noticed that the subjective pain sensation measured by VAS and NRS in healthy subjects does not truly follow the physiological measurements. For instance, some patients scored high pain on the VAS and NRS scales without having any visible sign of pain and vice-versa [12]. It was a priori understood that experimental pain reflected only a part of the multidimensional, complex pain experience that could not be compared directly to clinical pain. To overcome confounders of the experimental system in healthy volunteers and to validate the results from this study it is necessary to collect data from patients experiencing real life pain. In the future, a new study with postoperative pain patients will be performed. The new study design will focus on continuous collection of physiological data in a non-invasive way from patients and their opinions on their pain.

One limitation of the study is the low number of healthy subjects and observations, which in turn limits the generalizability of the method. Due to this limitation, we could not compute correlations during the CPT since we had two observations (baseline and intervention) per subject. Additionally, this limited us to employ machine learning on the data and to try to relate features extracted from the multiple sensors with the VAS and NRS.

In conclusion, the results from this study indicated that the method could objectively detect pain periods in subjects with experimentally induced pain by a thermal stimulus.

Further evaluation is needed to assess its validity and reliability for continuous and personalized assessment and treatment of pain with opioids.

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