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On The Use of Evoked Potentials for Quantification of Pain

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Abstract – **Pain is a subjective and individual sensation causing major discomfort. So, it is necessary to put into practice methods to objectively quantify it. Several studies indicate that evoked potentials (EP) generate responses which may reflect painful processes. This study reports the results of the application of two different protocols by using biopotentials to objectively measure pain. The first (protocol 1) evaluates the relation between pain, induced by electrical stimulation, and subjective perception and also with nociceptive flexion reflex (NFR) represented by muscle activity (electromyography) detected on the femoral biceps after sural nerve stimulation. The second protocol (protocol 2) verifies whether there is some correlation between M-wave parameters and subjective pain sensation. The results obtained from protocol 1 suggest that the area of the EMG envelope and entropy estimated from the EMG activity are correlated with subjective sensation of pain. The analysis of data obtained from protocol 2 shows a correlation between the global minimum of the M-wave and pain increase. These results contribute to studies which seek to objective measures for pain quantification based on the analysis of biopotentials.**

Keywords – Electromyography; Pain; M-wave; Nociceptive Flexion Reflex

I. INTRODUCTION

According to IASP (*International Association for the Study of Pain*) pain is defined as an emotional and/or sensitive experience that may be associated to a real or potential tissue injury [1]. Thus, pain definition depends on human experience [2].

Lacert and Shah [3] say that pain is always a subjective phenomenon, and this interfere on its direct and objective measure. Studies seeking to the quantification of pain face problems such as the influence of anxiety, the level of motivation of the subject and the somatic and autonomic reflexes that may be triggered by other phenomena which are independent of pain [4]. Besides, the determination of the origin, severity and experience of pain is frequently based on subjective individual experiences [3].

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Clinical assessment may help in the stablishement of pain intensity. Therefore, it is a practical way for evaluating the effectiveness of the effect of drugs and other therapies [5]. There are some psychophysical methods that can be used to quantify pain, for example, the McGill questionnaire, numeric and verbal scales, and also the visual analog scale (VAS) [2, 6, 7]. However, in some clinical cases, such as when patients have limited communication capacity, the use of such instruments may not be adequate [7].

According to Chan and Dallaire [8], it is desirable to validate the pain measurement through psychophysical instruments and physiological measurements simultaneously.

The nociceptive flexion reflex (NFR), which is evoked from electrical stimulation has been proposed as a physiological nociceptive indicator [4, 8, 9]. The NFR is typically assessed when monitoring the muscle activity of the femoral biceps, when the sural nerve is electrically stimulated [4, 10].

The required stimulation intensity to elicit the NFR is used as an objective indicator for nociceptive threshold, and it has been used in clinical and experimental studies related to pain modulation analysis [9, 10].

Another physiological response that may be related with pain is the M-wave, which is a muscle action potential evoked by a motor nerve stimulation [11]. This wave may be evoked by stimulating peripheral nerves with needle or surface electrodes placed on the skin, upon the motor point [12].

As discussed by Skljarevski and Ramadan [13], it is important that researches that seek the development of tools for the measurement of pain consider the use of experimental protocols which allows for stable measurements and the reduction of subjective variables on the experiment.

In this context, this study seeks to verify whether there is a correlation between the stimulus intensity, pain subjective perception and nociceptive flexion reflex. For this, two experimental protocols (Protocol 1 and Protocol 2) were designed and evaluated.

II. METHODOLOGY

Protocol 1

Ten healthy male subjects, aged between 20 and 27 years, were involved in the experiments. Data collection was executed at the Laboratory of Biomedical Engineering (Biolab), Federal University of Uberlândia, Brazil. The study was approved by the Ethical Committee of the Federal University of Uberlândia. Before participating in experiments subjects signed a Consent Form.

In this experiment the electrodes to capture the EMG signal were fixed with the aid of an adhesive tape in the right femoral biceps. One electrode was positioned 10 cm above the popliteal fossa on the muscle, according to France, Rhudy and McGlone [10] and the volunteer remained in the

prone position. The other EMG electrode was placed on the skin over the right extensor digitorum brevis. The EMG reference electrode was positioned at the head of the right fibula.

The painful stimulus was caused by electrical stimulation of the external right retromalleolar sural nerve, posterior to the lateral malleolus.

For electrical stimulation, the cathode was positioned on the outer track of the retromalleolar right sural nerve and the reference electrode for the electrical stimulation (anode) was positioned proximally to the right medial malleolus. These were disposable electrodes (Meditrace Ag / AgCl), of 1.5 cm in diameter.

The parameters set in the stimulus equipment Neuropack S1 MEB-9400, Nihon Kohden, were as follows: 5 rectangular pulse trains with 0.2 ms and 10 ms interval between pulses.

The data collection started 100 ms before the electrical stimulation and finished 200 ms after it. It is important to analyze the period before electrical stimulation since the appearance of the flexion reflex is involuntary and could be present.

The component of flexion RIII reflex that is evaluated in this study is the long latency and appears of 85 to 120 ms after the stimulus [14, 8].

It was determined the threshold of perception of the volunteer by the method of limits [15]. The pain tolerance level of the subject has been found by gradually increasing the intensity of stimulation to the maximum tolerable limit, by using the Visual Analog Scale (VAS) (Figure 1).

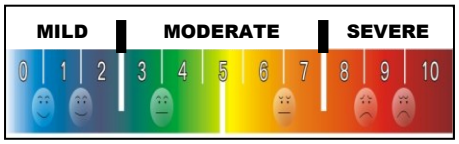

Figure 1: Visual Analogic Scale of Pain

The VAS allows for the volunteer to quantify his/her pain from 0 (no pain) to 10 (maximum bearable pain). These intensities of threshold stimulation and tolerance were normalized to 0% and 100% respectively.

Eleven stimulus intensities, linearly spaced between 0% and 100%, were employed in the study. Each subject was stimulated 10 times, for each stimulus intensity, and the obtained responses for each stimulus intensity were averaged.

These data (average responses) were saved in a text file and analyzed in MatLab. The approximate entropy, the area and the RMS (root mean squared) were estimated from the EMG signal (evoked response). These features were correlated with the VAS and with the intensity of the electrical stimulus.

The approximate entropy was evaluated by means of electromyographic signal, 100 ms before (PreEn) and 200 ms later (PosEn) of electrical stimulation. For data analysis, the values reported by the volunteer in the VAS were multiplied by 10. The statistical analysis was based on Pearson's correlation coefficient (r), coefficient of determination (r2) and linear regression.

Protocol 2

After the approval of the Research Ethics Committee, Federal University of Uberlândia (UFU), protocol 036/09, this study was carried out with 13 healthy individuals, being 6 males and 7 females, aged between 18 and 30 years. Data were collected in the Laboratory of Biomedical Engineering (Biolab) of the university.

Inclusion criteria were no history of surgery, dominant lower limb pain or injury. Exclusion criteria were the presence of central or peripheral neurological disorders and rheumatic impairment; use of pacemaker or heart problems; obesity; use of drugs changing motor control and peripheral sensitivity, such as benzodiazepines, opioids, anti-histaminics, anticonvulsants and antidepressants; lower limb amputation and diabetes mellitus.

Each volunteer participated in five experimental sessions. All sessions were carried out in the same period of the day due to possible Circadian rhythm influences. During the experiments, volunteers remained comfortably in the supine position in a reclining chair, with plantar ankle flexion and foot inversion. Dominant foot was used. Before positioning the electrodes, skin was cleaned with alcohol and, when needed, it was shaved. The reference electrode of the electrical stimulation was fixed at the lateral foot margin and electrical stimulation electrode was placed at the medial foot margin, at the motor point of the abductor hallucis muscle.

In order to detect the motor point of the abductor hallucis muscle a pen-shaped electrode was used which was slid over the medial foot margin simultaneously with electrical pulses emission. The point with the maximum mechanical response with minimum current was considered the motor point of the abductor hallucis muscle.

EMG electrodes were fixed between the motor point and the distal muscle tendon, with the reference electrode positioned on the medial malleolus of the same limb. The EMG signal capturing electrode and the reference electrode were fixed with tapes specific for this purpose (Figure 2).

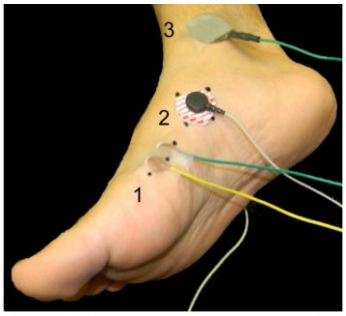

Figure 2: Positioning of electrodes on foot medial margin. (1) EMG electrodes, (2) Electrical stimulation electrode, (3) EMG reference electrode.

To ensure that EMG and electrical stimulation electrodes were positioned at the same place during the five days of test, each electrode received a staining layer which remains on the skin for approximately one week, popularly known as henna.

Tolerance level of research subjects was assessed by gradually increasing stimulation intensity until the maximum supportable limit using VAS, and the volunteer verbally

indicated pain perception from zero to 10, being zero no pain and 10 maximum tolerable pain.

Volunteers received stimulations of 20 pulses of 2 Hz and 0.3 ms as from 1 mA. After each series of 20 pulses, volunteers reported pain intensity perceived according to VAS and made observations they considered necessary for the researcher. After volunteers' report, other 20 pulses were emitted with 1 mA increments and so on, until volunteers reported pain intensity equal to 10.

During each 20 pulse session, the researcher recorded pain perceived by the volunteer on a table according to VAS and also reported observations. The researcher had also the menstrual cycle period for females.

Electrical stimulation and electromyographic data were recorded with the Neuropack S1 MEB-9400 equipment, from Nihon Kohden, Japan.

M-wave data were stored in text format (.txt) and analyzed by customized programs developed in MatLab (MathWorks). From these programs, it was possible to estimate the following M-wave parameters: minimum and maximum peak and time when they occurred. Each parameter was correlated to pain sensation reported in VAS.

Preliminary evaluations showed that only the minimum peak, that is, M-wave global minimum, was correlated to pain sensation and so, only results with correlation with pain sensation were considered.

III. Results

Protocol 1

It was observed that there was a strong positive linear correlation of VAS with the electrical stimulus. The PreEn showed a weak negative linear correlation and PosEn a strong negative linear correlation.

The area showed strong positive linear correlation with respect to the applied stimulus and the RMS. Table I, given below, shows the values of the Pearson's correlation coefficient (r), the straight line equations from the linear regression and the coefficient of determination (r^2), respectively.

Data were analyzed using all the group of subjects.

TABLE I
Statistical Parameters

Feature	Pearson's correlation coefficient (r)	Straight line equation	Coefficient of determination (r^2)
Area	0.974094	y = 0.3559x + 16.971	0.9489
PosEn	-0.93315	y = -0.2433x + 60.415	0.8708
VAS	0.998307	y = 0.5502x + 18.011	0.9966
RMS	0.97	y = 0.321x + 20.333	0.946

Protocol 2

Figure 3 shows a typical example found for the relationship between applied current value (in mA) in the X-axis and minimum M-wave peak value (in µV) in the Y-axis. The overall mean of the current values in mA in which volunteers have reached pain threshold was 16.8 for male subjects and 14.9 in female subjects, pain tolerance was reached 36.5 mA and in 31.2 mA for male and female respectively, it shows that men's tolerance to pain is higher than women tolerance. No significant difference were found among the different phases of menstrual cycle in the tests of each woman.

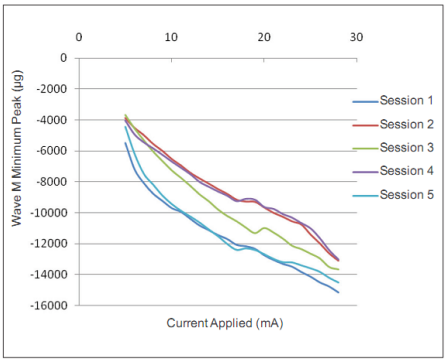

Figure 3: Relationship between M-wave minimum peak and applied current. Note that this result is from a specific subject but it is typical.

IV. Discussion

Protocol 1

The technique used for recording the electrical signals from the biceps femoris muscle before and after the painful stimulus was the EMG. Several authors [4, 8, 9, 10] make use of this technique in studies involving pain.

It was verified that there was a strong positive linear correlation analysis of VAS with the electrical stimulus. The research of Chan and Dallaire [8] also showed a linear correlation between VAS and stimulus intensity, in other words, with increasing intensity of the stimulus volunteers reported a higher score for the VAS.

Another feature evaluated in this study was the approximate entropy before (PreEn) and after (PosEn) electrical stimulation. As expected the PreEn feature was weakly correlated with pain, whereas the PosEn feature was highly correlated.

The analysis of the correlation between the area with the stimulus showed a strong linear correlation, which confirms the results obtained by Chan and Dallaire [8]. So the area of the EMG signal was higher with increasing intensity of electrical stimulation that caused the pain.

Regarding the RMS, it showed a strong positive linear correlation with the percentage of the stimulus. This correlation is high in the period of 200 ms after electrical stimulation and it is not noted in the 100 ms period before stimulation.

Protocol 2

There is major correlation between M-wave minimum peak decrease and increased intensity of the current applied to individuals, both males and females. Results were as expected, showing a strong correlation between minimum peak and increased current, consequently with increased pain.

In comparing males and females, it was observed that mean pain threshold value was higher for males.

In comparing males and females, it was noticed that current value needed to reach maximum pain value was higher for males (36.5 mA) as compared to females (31.2 mA).

Both protocols used VAS to correlate subjective pain and the physiological parameters. VAS is used in many protocols and objective methods are needed to quantify pain.

V. Conclusion

Protocol 1

The features PosEn, RMS and area of flexion reflex are relevant parameters for the quantification of pain. The identification of these features may be used in more complex algorithms and tools for the automatic procedure of pain quantification.

Protocol 2

M-wave global minimum has shown to be correlated with pain sensation increase, and in males pain threshold and tolerance were higher than in females. Different menstrual cycle phases have not interfered with evaluations.

In general, we can conclude that both protocols are able to, objectively and in a safe way, evaluate pain and other studies are needed to consolidate it. Both protocols were used just in healthy subjects since subjects with previous pain and muscle impairment were excluded from the tests and the results of the use of the protocols in non-healthy subjects is still unknown.

And now we can see that biopotentials may be, in a near future, a new way to objectively quantify pain.

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