БІОЛОГІЧНІ ТА МЕДИЧНІ ПРИЛАДИ І СИСТЕМИ

UDC 004.9

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STUDYING IMPACT OF PAIN TO HEART RATE VARIABILITY

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Abstract. The method of pain estimation based on some heart rate variability parameters was proposed. Software for calculating these parameters was developed. A positive correlation between RMSSD/SDNN ratio and HF/LF ratio with pain level was obtained. The use of this method in resuscitative medicine and in combat operations is suggested.
Key words: heart rate variability, pain, software development.
Анотація. На індивідуальне сприйняття болю впливають демографічні фактори, стать, вік, етнічні особливості, а також емоційний і фізичний стан пацієнта. Більш об'єктивні методи оцінки болі ті, що засновані на кореляції між певними фізіологічними показниками людини та ступенем больового синдрому. Розроблено інформаційного засобу (програми) для дослідження впливу больового синдрому на різні показники варіабельності ритму серця (ВРС), такі як RMSSD, SDNN, LF, HF, Coherence Ratio.Були проведені клінічні дослідження у Головному військовому клінічному госпіталі міста Києва. Знято ЕКГ 18-ти пацієнтів в різному стані. Після зняття ЕКГ пацієнтів оцінювали рівень болю за вербальною оціночною шкалою. Отримані записи ЕКГ було оброблено програмою HRV Analyzer, розробленою в контексті цієї роботи.
Найкраща кореляція з рівнем болю у показника HF/LF – 76%. Також висока ступінь кореляції у показника RMSSD/SDNN - 74%. Показник когерентності має найгіршу кореляцію – 42%. Отже знайдено інтегральний показник ВРС, що дозволяє оцінювати рівень больового синдрому та може використовуватися в екстренній медицині, реанімації, реабілітації, під час бойових дій тощо.
Ключові слова: варіабельність ритму серця, больовий синдром, програмне забезпечення.
Аннотация. На индивидуальное восприятие боли влияют демографические факторы, пол, возраст, этнические особенности, а также эмоциональное и физическое состояние пациента. Более объективные методы оценки боли те, что основаны на корреляции между определенными физиологическими показателями человека и степенью болевого синдрома. Разработана программа для исследования влияния болевого синдрома на различные показатели вариабельности ритма сердца (ВРС), такие как RMSSD, SDNN, LF, HF, Coherence Ratio. Были проведены клинические исследования в Главном военном госпитале города Киева. Снято ЭКГ 18-ти пациентов в различном состоянии. После снятия ЭКГ пациентов оценивали уровень боли по вербальной оценочной шкале. Полученные записи ЭКГ было обработано программой HRV Analyzer, разработанной в контексте этой работы. Лучшая корреляция с уровнем боли у показателя HF / LF – 76%. Также высокая степень корреляции у показателя RMSSD / SDNN - 74%. Показатель когерентности имеет худшую корреляцию – 42%. Итак, найдено интегральный показатель ВРС, что позволяет оценивать уровень болевого синдрома и может использоваться в экстренной медицине, реанимации, реабилитации, во время боевых действий.
Ключевые слова: вариабельность ритма сердца, болевой синдром, программное обеспечение.
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Introduction

The determination of the pain syndrome intensity and the changes of this intensity in time are important tasks in the practice of extreme conditions medicine, especially military medicine.

Recent guidelines on the management of pain, agitation, and delirium in adult patients recommend a systemic and rigorous evaluation of pain in critically ill patients, particularly because pain is consistently undertreated in this population [1]. Whilst evaluation of pain could be helpful in improving patient comfort and avoiding over sedation, this could be a difficult task in sedated non-communicative critically ill patients. Behavioral pain scale (BPS), and critical care pain observation tool (CPOT) provide acceptable levels of validity and reliability and are recommended for nonverbal pain screening. However, these scores have some limitations, including the inter-rater variability, their impossible use in patients receiving neuromuscular-blocking agents, and the discontinuous assessment of pain [2]. In addition, these scores take into account only the physical component of the pain and do not determine the level of anxiety and discomfort [3].

Adequate treatment of acute pain syndrome – one of the important ways to prevent a number of complications: thrombotic-embolus, respiratory, ischemic, etc., which reduces the length of hospitalization. Also, qualitative analgesia prevents chronic pain and the development of hyperalgesia.

Objective

The individual perception of pain is influenced by demographic factors, gender, age, ethnicity, as well as the emotional and physical condition of the patient. Existing pain level estimation methods require immediate contact with the patient, as well as the patient being in the mind.

Finding an objective, reliable, accurate, fast way to determine the intensity of the pain without the direct involvement of the patient began many decades ago. The most promising in this context is the analysis of the autonomic nervous state systems. The physiological basis of the method lies quite a well-known phenomenon of heart rate variability (HRV), which consists of the incidence of intervals between sequences of QRS complexes.

The variability of the cardiac rhythm decreases or disappears when brain deaths, myocardial infarction, diabetic dysautonomia, and some other diseases. It is known that the regulation of cardiac rhythm is the result of the rhythmic activity of the pacemaker cells of the sinus node, modulating effect autonomic and central nervous systems, humoral and reflexive influences. HRV depends on the tone of the autonomic nervous system under the influence of pain stimuli.

The task of this work is to develop method and software for evaluation of the effectiveness of HRV (heart rate variability) in the detection of pain in sedated, non-communicative, critically ill patients especially having combat trauma.

Method

Since the heart rhythm is a universal body response to any changes in the external environment. Some parameters of the heart rate variability (HRV) are indicators of vagal activity and may correlate with the level of pain [4], [5]. These parameters in the time domain are RMSSD (Root mean square of the successive differences) and SDNN (Standard deviation of R-R intervals) [6]. The SDNN indicator reflects the effect of both the sympathetic and parasympathetic nervous systems. The RMSSD is an indicator of vagal parasympathetic activity.

In the frequency domain, the analog of the SDNN indicator is the spectrum power in the low-frequency range from 0.04 Hz to 0.15 Hz, which is denoted as LF (low frequency) [7]. In the frequency domain, the analog of the RMSSD is the spectrum power in the high-frequency range from 0.15 Hz to 0.4 Hz, denoted as HF (high frequency). Accordingly, the HF / LF ratio is analogous to the RMSSD / SDNN ratio.

In a [8], research has shown that negative emotions such as frustration, anger, anxiety, and pain also result in such an incoherent model of the heart rate – that is, the heart rhythm varies greatly and is unpredictable (Fig. 1), at that time as positive emotions, on the contrary – are much more coherent and represent stable harmonic vibrations of the heart rhythm (Fig. 2).

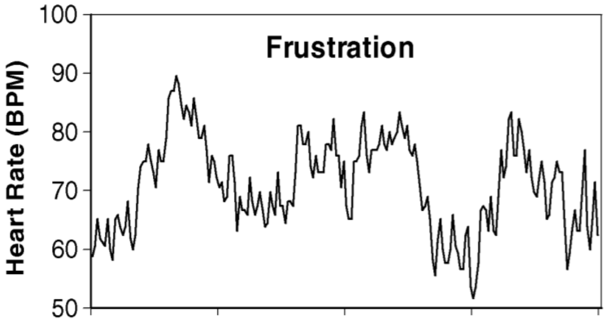

Figure 1 – Change of heart rate under the influence of negative emotions (in this case, disappointment) [5]

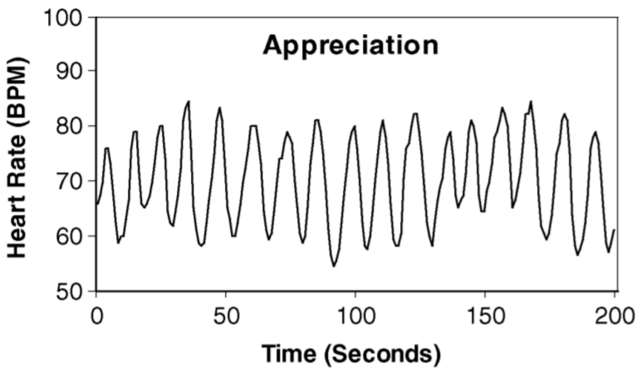

Figure 2 – Changing the heart rate under the influence of positive emotions (in this case – approval) [5]

In general, negative emotions and pain lead to less synchronization between the parasympathetic and sympathetic nervous system. Thus, the coherence approximates the ratio LF / (VLF + HF), where VLF is very low frequency (0.0033 Гц – 0.04 Гц).

Calculation of hrv parameters

A SDNN and RMSSD parameters

The standard deviation of R-R intervals (SDNN) is the integral characteristic of the autonomic nervous system (ANS) functioning [9]. This parameter depends on the activity of both the sympathetic and parasympathetic links of the autonomic nervous system; in particular, the increase in SDNN indicates an increase in parasympathetic nerve regulation, while the decrease is due to the growth of sympathetic effects and the suppression of the autonomous circuit activity.

$$SDNN = \sqrt{\frac{\sum_i (RR_i - \underline{RR})^2}{N}} \tag{1}$$

RMSSD (Root mean square of the successive differences) is an indicator of vagal-parasympathetic activity.

$$RMSSD = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n-1} (RR_{i+1} - RR_i)^2} \tag{2}$$

B Spectrum calculation

The best method to obtain a spectrum of HRV is the auto-regression method because it works even with a very limited amount of data and allows for clear, well-differentiating peaks in the spectrum. There are also several algorithms for calculating the autoregressive model. The developed software implements the Yule-Walker algorithm and the Burg algorithm. Both give similar results. The optimal order of the model is calculated automatically according to criteria AIC (Akaike Information Criteria) [10].

C Calculation of Coherence Ratio

According to [8], the peak of coherence is called the peak on the HRV spectrum in the frequency range from 0.04 Hz to 0.26 Hz. The algorithm for calculating the coherence ration is the following:

1. Find the largest peak on the spectrum in the frequency range from 0.04 Hz to 0.26 Hz.
2. Calculate the peak power in a 0.015 Hz window above and below the peak frequency.
3. Calculate of total spectral power (from 0.033 Hz to 0.4 Hz).
4. Calculate the coherence ratio using the following equation:

$$Coherence = \frac{PP}{TP - PP}; \tag{3}$$

where PP is the power of the peak of coherence, TP is the total power of the spectrum.

Software development

For this project, special software was developed in the C # programming language for heart rate variability analysis. The developed software has the following functionality [11]:

- *Calculation of basic HRV time-domain parameters*
  Calculation of typical HRV parameters such as heart rate, SDNN, RMSSD, pNN50, and others.
- *Calculation of the R-R intervals distribution histogram*
  The histogram allows the user to visually estimate the distribution of R-R intervals. A duration of "bin" on histogram can be determined both automatically and manually.
- *Interpolation of R-R intervals*
  A raw set of R-R intervals is not suitable for frequency domain analysis because it is not equidistant in time. It is necessary to interpolate this series with a constant time step in order to correctly apply frequency analysis algorithms. The standard for HRV analysis is an interpolation with a 4 Hz sampling frequency. This is enough to build a spectrum up to 2 Hz. Cubic spline interpolation was implemented in our software.
- *Calculation of the power spectral density by Fourier transform*
  Fourier method with different window functions. Input data are multiplied by a window function. The type of window function can be selected from the list. By default, the Gaussian window function is used, which allows you to vary the smoothing using the alpha parameter.
- *Calculation of the power spectral density by Autoregression method*
  Autoregression method is more suitable for HRV analysis, because it works even with very limited data, and allows for clear, well-differentiated peaks in the spectrum. There are also several algorithms for calculating the autoregressive model. The program implements the Yule-Walker and Burg algorithms. Both give similar results. The optimal order of the model is calculated automatically according to the Akaike Information Criteria, but it can also be set manually.

Flowchart of HRV Analyzer processing is shown in fig. 3:

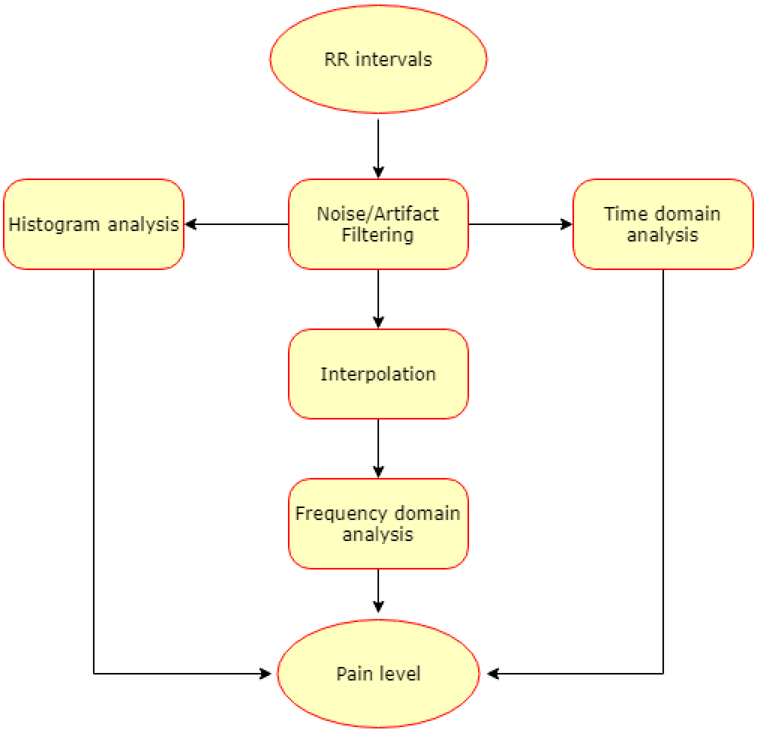

Figure 3 – Flowchart of the algorithm of software data processing

A screenshot of the software window with target HRV parameters (RMSSD/SDNN, LF/HF, Coherence) is shown in fig. 4.

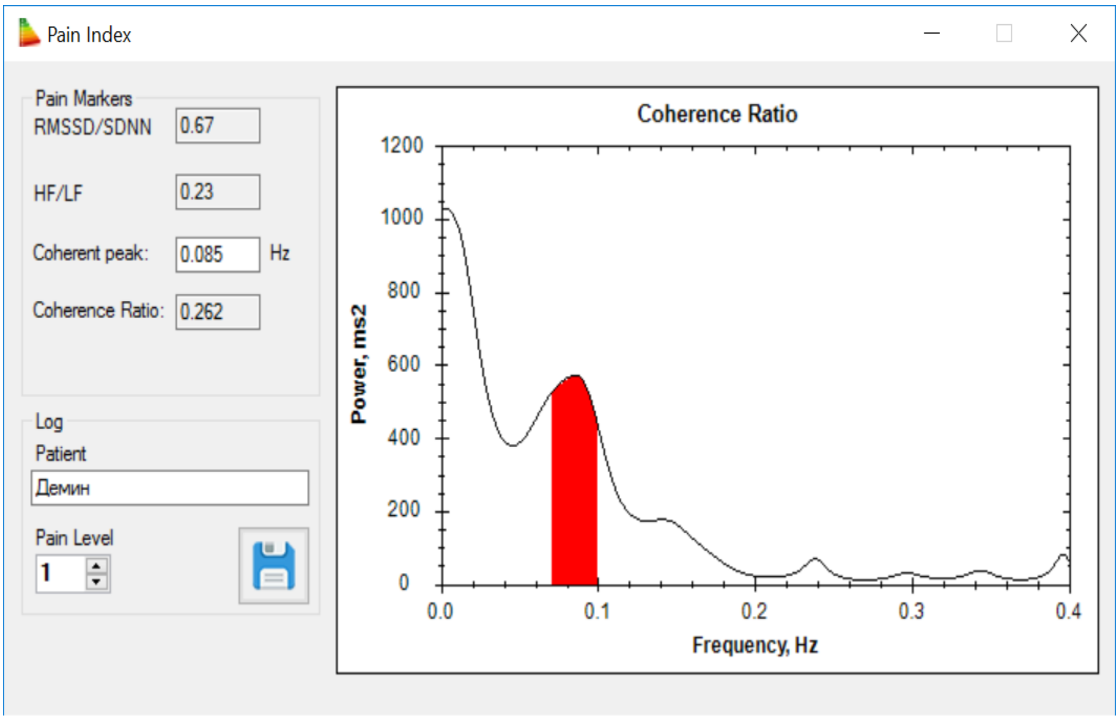

Figure 4 – Screenshot from HRV Analyzer software. Here are HRV parameters correlated with pain level

Clinical trials

Clinical trials were performed in the Kyiv Military Hospital to check the correlation between selected HRV parameters and the level of pain.

Clinical studies have been made in accordance with modern international standards and other regulations for medical devices and clinical trials including ethics of experimentation in accordance with the Declaration of Helsinki.

ECG signals were recorded in different states from eighteen servicemen and volunteers having combat trauma during military conflict with pro-Russian terrorists in East Ukraine. Age and gender profile of examined patients are shown in Table 1.

Table 1 – Age-gender distribution of examined patients

Age group	Male	Female	Total
18-39	3	1	4
40-59	6	4	10
60+	2	2	4
Total	11	7	18

Despite the fact that amount of examined patients are small, it is still valuable. As shown in paper [11] with very low variance, both false positives and false negatives occurred at sample size(N) $N < 8$, but data shape was always clearly identified at $N \geq 8$. With high variance, accurate inference was stable at $N \geq 25$. In our model we use linear regression, which is a model with low variance, so our data set size (18 patients) is enough to obtain informative results.

The duration of each record was 3 minutes. After ECG recording, patients evaluated the pain level according to the verbal scale (no pain – 0 points, weak – 1 point, moderate – 2 points, strong – 3 points, strongest – 4 points) [12].

The received ECG recordings were annotated by the PulseWave software developed at the Kyiv Institute of Cybernetics. The received annotations (the sequence of detected ECG waves (P, Q, R, S, T)) were imported into the HRV Analyzer software developed by the authors and HRV parameters were calculated.

Dependency between HRV parameters and subjective pain level are shown on figures 5–7.

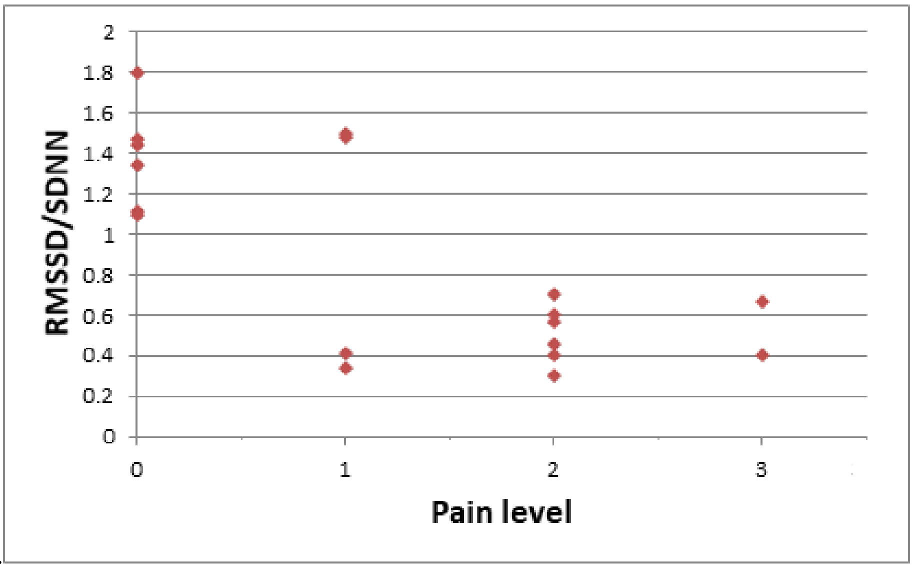

Figure 5 – Dependency between RMSSD / SDNN and pain level

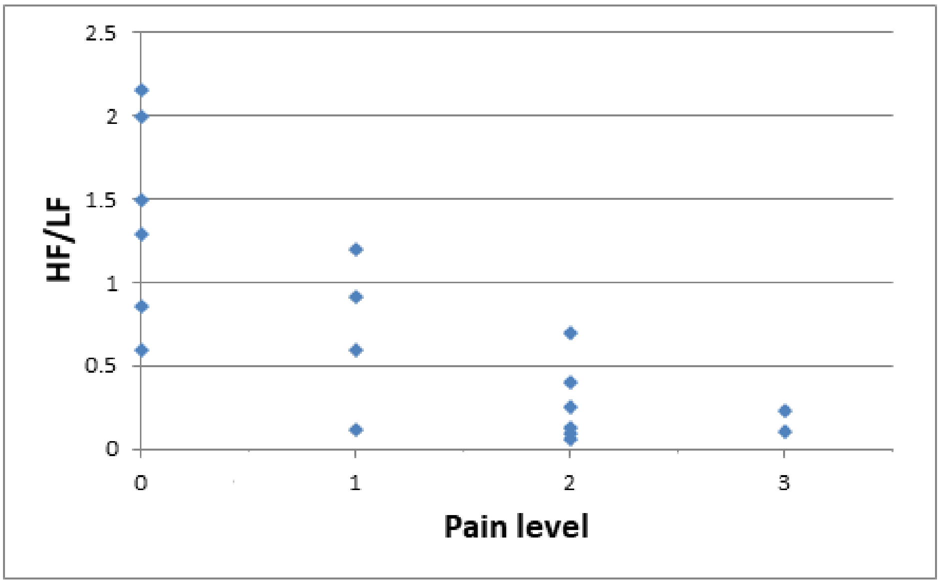

Figure 6 – Dependency between HF / LF ratio and pain level

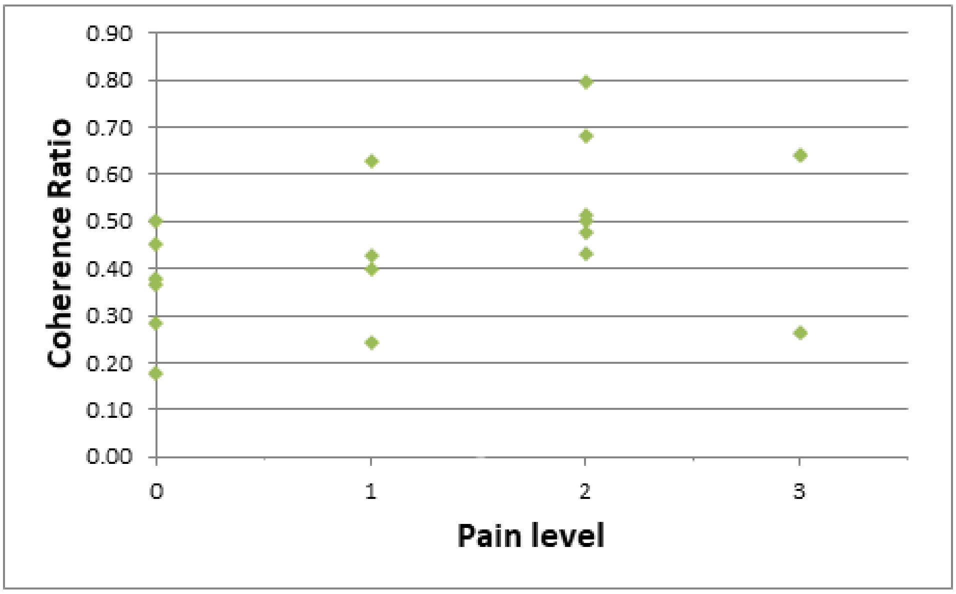

Figure 7 – Dependency between coherence ratio and pain level

The figures show that the HF / LF is the best correlate with the pain level. Correlation coefficients were also calculated:

$$R_{\frac{RMSSD}{SDNN}} = 74\%; \qquad R_{\frac{HF}{LF}} = 76\%; \qquad R_{Coherence} = 42\%;$$

Thus, it is clear that the best result gives an assessment of the pain syndrome by the HF / LF index, and a bit worse – by RMSSD / SDNN. It should be noted that in order to more accurately select the best indicator for assessing the level of pain, clinical trials should be conducted in more patients to reduce the statistical error.

On the basis of these data, a linear regression model was constructed, according to which the pain level can be estimated with the following expression:

$$Pain = 2.54 - 0.63 * \frac{RMSSD}{SDNN} - 0.88 * \frac{HF}{LF} - 0.38 * Coh \tag{4}$$

The calculated overall pain index has a correlation coefficient of 77%.

Results and discussion

We have proposed an original index for determining the intensity of pain syndrome based on estimating the power of high-frequency oscillations, others in words – the strength of vagal influence on the variability of the heart rate.

This algorithm is implemented in the software "HRV analyzer" developed within the project IK-2015/2 "Development of Portable software-hardware complex to determine the depth of the shock state in the field conditions for military medicine" within the framework of the Target Research Program of NASU "Research and development for increasing the defense and security of the state" (2015–2016).

Indicator of the intensity of pain is calculated on the basis series of intervals R-R after their filtration and normalization.

The analysis consists of five steps:

1. ECG signal filtration and correction of false QRS complexes (eg extrasystole replaced by an artificial complex R);
2. Extraction of RR-intervals from ECG (time intervals between normal QRS complexes;
3. HRV analysis
4. Identification of signs related to pain;
5. Calculation of the intensity index of the pain syndrome.

Conclusion

The method of assessing the pain level according to the following HRV parameters:

a. RMSSD / SDNN;
b. HF / LF;
c. Coherence ratio.

Calculation of coherence ratio using the autoregressive model and use RMSSD / SDNN as an indicator of pain level is new in the HRV analysis field. A software tool has been created to calculate the above HRV parameters.

Preclinical trials have been conducted, the result of which is the calculated integral HRV index, which correlates with a subjective pain level at a 77% level.

Finally, the result of the work is an integral HRV index, which estimates the level of pain and can be used in clinical medicine, resuscitation, during rehabilitation, combat medicine, etc. We believe that optical-based pulsometric devices are a promising tool instead of an ECG recorder for HRV signal recording [13], especially for long-time monitoring [14].

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ДОСЛІДЖЕННЯ ВПЛИВУ БОЛЬОВОГО СИНДРОМУ НА ВАРІАБЕЛЬНІСТЬ РИТМУ СЕРЦЯ

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ИССЛЕДОВАНИЕ ВЛИЯНИЯ БОЛЕВОГО СИНДРОМА НА ВАРИАБЕЛЬНОСТЬ РИТМА СЕРДЦА

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