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Automated system for measuring integral pain index of patients during general anesthesia

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***Abstract* — For optimal control of the analgesia level during general anesthesia an objective assessment of the realtime patient's current state is necessary. Such estimates are based on the production and processing of large amounts of data. The authors developed requirements for an automated system for measuring the level of pain experienced by patients during anesthesia, methods and algorithms for implementing such a system. To assess the patient's condition, a set of indicators is used: flow data on the respiratory cycle of the patient, the spectral characteristics of the electroencephalogram and electrocardiogram; indicators of electrical conductivity of the skin; characteristics of the pulse wave; dynamics of changes in mean blood pressure, heart rate. The article presents a block diagram of the operation of the module for calculating the integral indicator of pain and shows the results of preclinical tests.**

Keywords — general anesthesia, automated system, pain index, sedation level, ARX model, hemodynamic parameters

I. Introduction

When performing complex surgical operations it is necessary to use anesthesia. For competent decision making, the anesthesiologist must in real time analyze large volumes of information about the patients' condition. The correctness and timeliness of the decisions made by the anesthesiologist may be critical for the life and health of the patient.

Therefore, important to create a comprehensive automated system for measuring and analyzing patient information, designed to reduce the informational and intellectual burden on the anesthesiologist; reducing the number of his mistakes. A key aspect for performing balanced anesthesia is measuring the current levels of sedation and nociception. Both of these parameters can be quantified based on measured parameters of the patient's condition during surgery.

The level of sedation (depth of anesthesia) is the dynamic balance between the loss of consciousness by the patient and the intensity of surgical stimulation.

Unconsciousness is characterized by the absence of patient movements, awareness, and immunity to painful stimuli. The intensity of surgical stimulation depends on the type and duration of the operation [1]. The level of sedation can be determined by analyzing the electroencephalogram (EEG) and the subsequent calculation of the bispectral index (BIS) or AAI index (A-line ARX Index) [2]. The details of the algorithm for calculating the BIS index by the company Aspect Medical Systems [3] were not disclosed. The AAI index is calculated by repeatedly applying the auditory stimulus to the patient and averaging the allocated EEG frames that follow each stimulus. Thus, the part of the EEG that is not associated with the response to the stimulus is eliminated, and specific evoked potentials are preserved, from the results of the analysis of which the degree of sedation can be calculated. High-frequency EEG signals (about 30 Hz) indicate that the patient is conscious, and low-frequency signals indicate a state of general anesthesia. Increasing the depth of anesthesia causes an increase in EEG regularity. It can be estimated by the value of entropy and used to calculate the depth of anesthesia.

To assess the level of sedation, the anesthesiologist can use the instantaneous values of changes in the frequency of the patient's EEG signals [4]. To obtain the instantaneous frequency and the instantaneous amplitude of the filtered EEG signal, the Hilbert – Huang transform is used. It is best suited for the analysis of non-stationary and non-linear data, such as physiological signals [5,6]. Values of instantaneous frequency, instantaneous amplitude and time of the filtered EEG signal can then be combined to create a three-dimensional representation of the EEG signal in real time. It can simultaneously express the amplitude and frequency of brain waves of the EEG signal and their change over time [4]. The moment when the patient loses consciousness during anesthesia is determined by a number of factors: the concentration of anesthetic drugs (AD); types of drugs used for sedation; gender, age, general condition of the patient; "sensitivity" of patients to drugs (differences in pharmacodynamics) and variability of drug metabolism in the body (differences in pharmacokinetics) [7,8,9]. This variability in the effective concentration of drugs is due to the variability of the physiological effects of drug effects on the body (differences in pharmacodynamics) and the variability of drug metabolism in the body (differences in pharmacokinetics) [10, 11]. Pharmacological variability of analgesics is significant and can reach 500% [12]. This does not allow to calculate before the operation the individual sensitivity a particular patient and the optimal dosage drug for him.

During the operation, the anesthesiologist uses numerous measured and calculated parameters describing the patient's condition (Table 1).

TABLE I. PARAMETERS OF THE PATIENT'S CONDITION, CONTROLLED BY THE ANESTHESIOLOGIST

Para-meter	Parameter name	Para-meter type	Used by the anesthesiologist to assess the pain experienced by the patient
DIA,SYS, APP	Diastolic, systolic, pulse, mean arterial pressure	Measu-red	
MAP	Mean arterial pressure	Measu-red	Yes
RR	Breathing frequency	Measu-red	
PR	Pulse frequency	Measu-red	Yes
HR	Heart rate	Measu-red	
NB	Neuromuscular blockade level	Calcu-lated	
BIS	Bispectral index	Calcu-lated	
AEP	Auditory evoked potentials	Calcu-lated	
SpO_2	Oxygen saturation	Measu-red	
T	Temperature	Measu-red	
IPVR	Peripheral vascular resistance index	Calcu-lated	
CI	Cardiac index	Calcu-lated	
Kj	Drug concentration in the blood	Calcu-lated	Yes
ANI	Analgesia Nociception Index	Calcu-lated	Yes

In addition, the anesthesiologist must take into account the trends in ECG, pulse and blood oxygen saturation observed on the monitor. All these parameters are used by the anesthesiologist to calculate the dosages and rates of administration of the drugs used: analgesic, neuroleptic, hypnotic and anesthetic. The state of the patient and the outcome of the operation as a whole depend on the accuracy of the choice of anesthesia and the dynamics of drug administration. However, only two indicators from Table 1 (MAP and PR) indirectly indicate the pain experienced by the patient.

The traditional method of assessing PI - tracking heart rate and mean arterial pressure. When these indicators change by more than 20% in 5-7 minutes, it is usually concluded that the patient perceives pain. However, the sensitivity of this method is considered to be not very high [13,14].

When using infusion dispensers to administer the analgesic, it is possible to estimate the current concentration of the drug in the blood and, based on this, to judge the current level of anesthesia. This method gives a very approximate result. Monitoring the current level of nociception is necessary to calculate the analgesic dosage.

Surgical stress reflects the balance between nociception (neural processes of coding and processing pain stimuli) and antinociception — a decrease in sensitivity to pain that occurs in neurons due to the use of analgesics. The choice of drugs and dosages for anesthesia is determined by the degree of trauma of the surgery, the patient's age, his body weight, current state, and concomitant pathologies. Doses of drugs are calculated by the anesthesiologist taking into account their pharmacodynamics and pharmacokinetics, clinical signs of overdose or insufficient concentration. At the same time, the issues of objective assessment and monitoring of the depth of analgesia and, consequently, assessment of the quality of analgesia [15, 16,17] are not fully resolved.

II. COMPARISON OF MODERN METHODS

We indicate only the most promising methods for determining the level of pain during anesthesia.

1) *Heart Rate Variability analysis*

Heart rate variability depends on the tone of the autonomic nervous system (ANS) under the influence of painful stimuli or the introduction of analgesics. Regulation of heart rate ANS is influenced by the respiratory cycle. Inhale temporarily suppresses the parasympathetic effect, causing acceleration of the heart rate and decreasing the RR intervals of the electrocardiogram. Exhale, on the contrary, stimulating the parasympathetic tone, slows the heart rate, increasing these intervals. Every breathing cycle followed by differences parasympathetic tone - respiratory sinus arrhythmia (RSA) [18,19,20]. In the absence of a painful stimulus and / or stress, only RSA affects the series of RR intervals. Therefore, analyzing the variability of the RR intervals, it is possible to determine the current level of nociception - it is the main indicator in calculating the need for doses of the analgesic, incl. in the above ANI Monitor [16,18]. The main disadvantage of this method is the use of data only the parasympathetic component of the ANS, which is influenced by other physiological factors.

2) *Skin Conductivity Analysis*

Assessment of the degree of pain (PI) and surgical stress is possible when measuring skin conductivity (SC), as a measure of emotional state or arousal. As shown in [21], surgical stress provokes a sympathetic nervous explosion. In this case, the palmar and plantar sweat glands are filled and SC increases. Then the sweat is removed and the skin conductance is reduced. Estimation of spontaneous changes in SC and the number of oscillations of SC per second in a patient is a rather effective method [22, 23]. The device that implements it contains the following modules: skin conductivity analysis; storage and processing characteristics of the signal conductivity. This allows using signaling means to indicate to the anesthesiologist that PI has reached a certain threshold [24].

3) Plethysmography method

Evaluation of PI using plethysmography is given in [25]. For the pulse wave (PW), a number of characteristics are distinguished (including the amplitude and position of the dicrotic notch, i.e. the incisuria). Then they are used to calculate of the PI index.

The main drawback of methods “2” and “3” is the use of data only from the sympathetic component of the ANS, which is also influenced by other physiological factors [18, 26].

4) Analysis of Brain Rhythms of Pain

The suppression of alpha and the amplification of the gamma rhythms of the EEG largely correlate with the pain load [27,28,29,30]. Evaluation of PI is made on the basis of changes in the spectral power before and during the pain exposure [31]

5) A multi-parameter approach

There are several methods that use various combinations of the above parameters [32,33,34]. For example, Medasense Biometrics Ltd. (Israel) [34,35] produces a non-invasive nociception monitor. The device integrates several physiological parameters, including heart rate (HR), heart rate variability, photoplethysmogram wave amplitude, skin conductance level, and number of skin conductance fluctuations, movements and their time derivatives to compute a real-time nociception index, called NOL. Four sensors (photoplethysmograph, Galvanic Skin Response, Temperature, and Accelerometer) are fastened on the finger of the patient. Data from sensors is processed using artificial intelligence algorithms. The pain scale of the NOL index varies from 0 (no pain) to 100 (intolerable pain).

An empirical algorithm for calculating the RN index was proposed in [32] for evaluating nociception based on the processing of ECG signal, state entropy (SE), response entropy (RE), Heart rate variability (HRV), photoplethysmography (PPG).

The authors of [33] developed the surgical stress index (SSI). SSI was computed as a combination of normalized heartbeat interval and plethysmographic pulse wave amplitude.

These studies have shown that a combination of several parameters related to nociception allows a more accurate assessment of the patient's condition during surgery. However, each of the combined methods considered has its limitations. NOL does not use an electrocardiogram to analyze heart rate variability. However, with the help of an ECG, the variability of the R-R interval can be tracked with high accuracy, especially when it comes to a not very strong nociceptor effect or when we deal with sufficient compensation with the help of analgesics. In addition, the registration of the level of conductivity and the number of fluctuations in the conductivity of the skin is most effectively measured on the inside surface of the palms, and not on the finger. The NOL index also does not take blood pressure into account. Nevertheless, this index showed good experimental results on the assessment of nociception. The RN and SSI indices do not include skin conductance level and a number of skin conductance fluctuations.

Therefore, it is necessary to develop an integrated pain index (IPI), in which it will be possible to take into account more informative parameters for assessing the patient's condition during anesthesia.

III. Requirements for Integral Pain Index Assessment System

The main principles used by the authors for quantitative assessment of PI: achieving maximum measurement accuracy, non-invasiveness, ease of use, monitoring in real time, the ability to use for patients of different ages, invariance to anesthesiology. Based on the analysis of scientific publications, patent search results and generalization of the anesthesiologist’s experience, to assess the level of nociception one should use the data of sympathetic and parasympathetic components of ANS, hemodynamics, characteristics of pulse wave (PW), EEG and ECG.

The spectral power and entropy of the respiratory cycle are calculated according to ECG. EEG data are used to analyze the spectral powers in the alpha and gamma ranges. Based on the skin conductance (SC), the rate of its change and the entropy of SC are calculated. Hemodynamic data are used to calculate the rate of change of the mean arterial pressure and a heart rate. The position of the dicrotic notch is calculated according to PW. Fig. 1 presents a functional block diagram of automated system for measuring IPI, developed by the authors

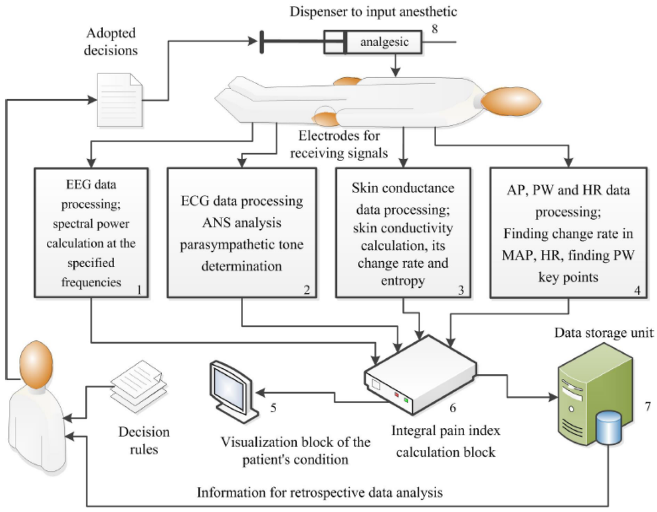

Fig. 1. Functional block diagram of system for measuring pain index (PI) of patient.

For the implementation of the proposed method, a few electrodes are used to collect EEG, ECG, skin conductivity (SC) data and a cuff for measuring blood pressure. Data from the EEG electrodes are received in block 1 (Fig. 1) for processing (amplification, filtering, removing artifacts) and calculating the spectral powers at given frequencies. Data from the electrocardiogram electrodes come to block 2, where they are amplified, filtered, removed artifacts, and the parasympathetic tone is calculated. In block 3, data are processed from the skin conductivity electrodes, and the rate of change in skin conductivity and the entropy are calculated.

In block 4, the rates of change in the mean arterial pressure (MAP) and heart rate (HR) are calculated, the key points of the pulse wave (PW) are found. In block 6, based on the data obtained from blocks 1, 2, 3, 4 and the corresponding weights for these data, the calculation of the integral pain index (IPI) is performed. Then the IPI index is transmitted to block 5 for visualisation and to block 7 - for recording and retrospective analysis. The analgesic is entered through an infusion dispenser 8. The input speed and amount of the drug used is determined by the anesthesiologist based on current rules, recommendations, personal experience, current state the patient. The presence of the device defining the IPI index, will optimize the actions of the a anesthesiologist.

IV. Module for Calculating the Integral Pain Indicator (IPI)

In Fig. 2 a generalized description of a proposed procedure for calculating the integral pain indicator (IPI) is presented in the form of a functional block diagram. Data from the electrocardiogram electrodes are received in block 1 (Fig. 2), where they are filtered, rejection of artifacts and the calculation of the time of respiration. In block 2, the respiratory cycles are extracted from the continuous ECG signal using respiration data and the QRS component is replaced with a label corresponding to the R wave.

In block 5, the signal is analyzed for the presence of extrasystoles or arrhythmias. In their absence, data on the respiratory cycle is received to highlight the heart rate during inhalation (block 10) and exhalation (block 11). If there are arrhythmias or extrasystoles in the respiratory cycle, the signal undergoes reconstruction. Blocks 3, 4, 6, 7, 9 are used for this. Then the signal in the "restored" form gets into block 8, where it is assigned a label - "quality indicator". When the signal is restored, the extrasystole is eliminated, and the R marker is "set" at the calculated place. At the same time, the signal quality criterion decreases. The ARX model is used to calculate the installation location of the R marker (block 6). Its inputs receive averaged data for the last respiratory cycles: ten (block 3) and three (block 4). In block 7, the order of the ARX model is adjusted based on the minimum simulation error If the "quality indicator" drops below a predetermined, then respiratory cycle, it is excluded from processing (block 12), since the ARX model cannot predict the elements of this cycle with acceptable quality.

The definition of parasympathetic tone occurs in block 13 - based on the data on heart rate during inhalation and exhalation. Unit 15 calculates the spectral power at inhalation and exhalation frequencies. Block 16 performs the calculation of spectral entropy. It describes the irregularity, complexity of the signal. For example, a signal that periodically alternates between two fixed amplitudes is fully predictable and has an entropy value of "0".

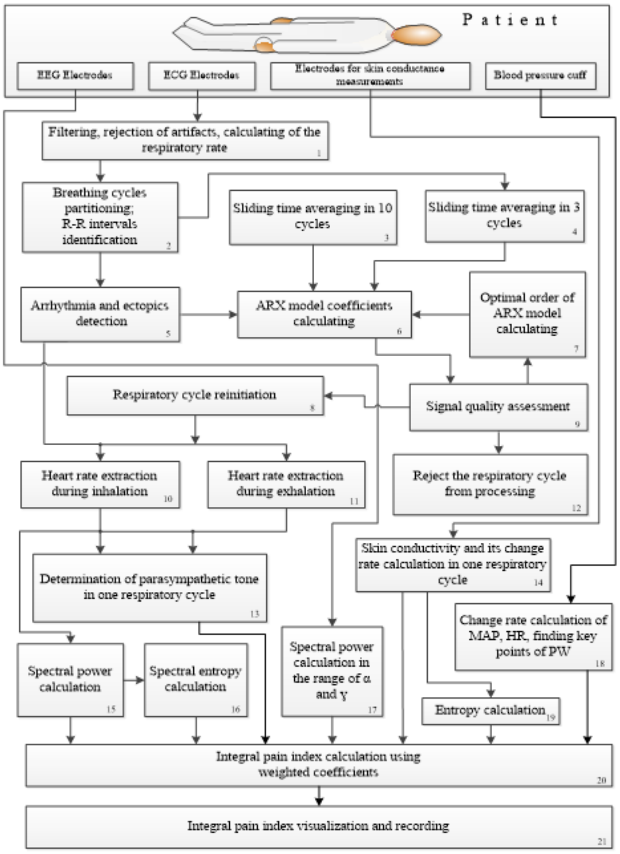

Fig. 2. The block diagram of the module for calculating the integral pain indicator (IPI)

On the other hand, the signal that is generated by some random process has greater complexity and greater entropy. And then entropy does not depend on the absolute scale of the measured quantity (amplitude and frequency). Additionally, the use of entropy can detect non-linear signal features [36, 37]. The data from the EEG electrodes arrive at block 17, where the spectral power is calculated in the alpha and gamma range. The results are transmitted to block 20, where weights are determined for them.

Electrodes for determining the skin conductivity (at a frequency of 200 Hz) are made in the form of pegs with fastening on the patient's palm. In block 14, the calculation of the SC and the rate of its change. In block 19, the calculation of the SC entropy.

In block 18, the calculation of the rates of change of mean arterial pressure, heart rate, characteristics of the pulse wave (the position of the dicrotic notch) is performed. Further, these data are received in block 20, where they are used to calculate the IPI, taking into account the dynamically changing weights. Their maximum values will be with severe cardiac disease and severe arrhythmias.

IPI is calculated by block 20. It can be used linear or logistic regression, fuzzy logic, neural networks or hybrid methods (combinations of the above). The calculation is performed using weighting factors and absolute values of the spectral power of the respiratory cycle (block 15), spectral entropy (block 16), spectral characteristics of the EEG (block 17), SC and its rate of change (block 14), entropy SC (block 19), data on the rate of change of the MAP, heart rate and PW characteristics. Block 21 is used to visualize, record data, build a trend of the dynamics of change over time in the IPI.

V. Preclinical Studies Results

The proposed method for the integral assessment of pain index (IPI) received a positive conclusion from the ethics committee of the Astrakhan State Medical University of the Ministry of Health of the Russian Federation (extract from the minutes of the meeting of the Ethics Committee No. 5 of November 6, 2018).

The proposed method has been clinically tested in the Department of Anesthesiology and Intensive Care at the Alexander Mariinsky Regional Clinical Hospital (Astrakhan, Russia). Below are the results of this testing during a planned laparoscopic cholecystectomy.

In the operating room, the following instruments were used to control the readings obtained by the proposed method for assessing the level of nociception during general anaesthesia: Mindray iMEC 12 monitor (for monitoring hemodynamic parameters and oxygen transport) and the monitor for auditory evoked potentials AEP™ (for monitoring the sedation level).

The pain level was recorded in three ways:

- by the proposed method for IPI determining;
- clinically-based, while continuous registration of peripheral hemodynamics;
- laboratory-based, while determination of serum cortisol level (enzyme-linked immunosorbent assay, ELISA using a BioTek ELx800 apparatus manufactured by BioTekInstruments Inc., USA).

At the traumatic stage of the surgical operation, the increase of average blood pressure and heart rate was recorded within the 10-15% range. The most pronounced hemodynamic response was 5-8 minutes after the maximum nociceptive effect.

The range of change of Integral Pain Index (IPI) is adopted from 0 (complete absence of pain) up to 10 (intolerable pain). For laboratory monitoring of the level of nociception, the authors analyzed the level of cortisol in the blood serum (nmol /L) and compared these values with the obtained IPI measurement results. Monitoring was carried out at the following stages: I - before sedation; II - after sedation; III - during the induction of anesthesia and intubation of the trachea; IV - at the traumatic stage of the surgical operation; V - at the end of the operation; VI - 30 minutes after completion of surgery. The comparison results are shown in Table 2.

Analyzing the above data, we can conclude that the adequate assessment of the pain index is quite achieved by the proposed method. It should be noted that the change in IPI occurs 30 to 40 seconds after nociceptive exposure, which allows the anesthesiologist to accelerate the decision about the optimal dosage of anaesthetic support.

TABLE II. Results of Experiment

Stages	I	II	III	IV	V	VI
The proposed method for nociception monitoring (index IPI)	2	2	4	7	6	3
Serum cortisol level (nmol / L)	480	509	630	748	650	590

VI. Conclusion

Based on the analysis of modern approaches to determining the level of nociception during general anesthesia, an optimal set of controlled and calculated parameters was obtained. It has been shown that when calculating the level of nociception (index IPI), the following should be considered: the condition of the ANS (parasympathetic and sympathetic components derived from an ECG analysis); EEG spectral power data in the alpha and gamma ranges; the rate of skin conductivity changing and its entropy; pulse wave parameters (diacrotic notch); the rate of change in mean arterial pressure and the number of heart contractions.

A flowchart has been developed for the operation of the IPI calculation module during general anesthesia. It allows to objectively assess the current IPI experienced by the patient. This, in turn, allows the anesthesiologist to determine the patient's operational need for an analgesic, the selection of its optimal dosage and speed of administration, and provides the optimal protection for the patient against surgical aggression. According to the results of the retrospective data analysis, it is possible for the anesthesiologist to evaluate the pharmacokinetic and pharmacodynamic properties of the drugs used.

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