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The new approach to calculation of physiological cost of activity: antinociception and normalization of the respiratory pattern of heart rate variability*

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Abstract. *Purpose* of this work is to propose an approach to the assessment of allostatic load based on the antinociceptive effect, which appears, obviously, due to changes in the activity of the endogenous opioid system (EOS); to compare the estimates obtained by measuring the pain threshold and calculating the index of respiratory effects on heart rate variability (HRV). The *method* of measuring the pain threshold is based on fixing the latent time of the thermonociceptive reaction (LTTR). The respiratory effect is measured by graphically determining the minimum normalized power of the fast HRV component in the range of 0.16...0.67 Hz, corresponding to the frequency of the respiratory pattern. *Results.* Based on small-volume experimental data (4 athletes and 4 episodes of physical activity), a quadratic two-factor regression equation was calculated for LTTR, respiratory effects factor and stress. A high correlation was demonstrated between the respiratory effect on HRV and the LTTR for one studied athlete. *Conclusion.* Using the example of sports, it is shown that it is possible to track the physiological cost of activities through LTTR. The inconveniences and subjectivity of the LTTR measurement procedure can be circumvented by replacing it with a normalized numerical index that considers the effect of breathing on HRV and the stress index. The proposed approach demonstrates the presence of reference values in the studied group, but requires further specially planned clinical studies.

Keywords: endogenous opioid system, antinociception, latent time of thermonociceptive reaction, normalization of heart rate variability, analgesia/nociception index, allostatic load.

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Introduction

This paper proposes a simple idea for standardizing the measurement of allostatic load (AL). Allostatic load is the essence of the physiological cost of a particular activity for the organism. When a reasonable level of AL is exceeded, a breakdown in adaptation and illness naturally occur.

The proposed method for assessing AL is based on measuring the exercise-induced antinociceptive effect, which occurs due to changes in the activity of the endogenous opioid system. The results obtained suggest the possibility of replacing the study of the pain threshold with a simpler (easily accessible) analysis of normalized heart rate variability (HRV).

Existing standard methods of HRV analysis [1–5] are ambiguous and require interpreter competence, artificial conditions for recording the cardiorhythmogram, an individual approach, dynamic observation and consideration of the activity context. The proposed method provides a normalized numerical index. The index is calculated based on the time domain analysis of HRV, revealing the respiratory effect on HRV. The logic of processing the cardiointervalogram (CIG) recorded by a mobile device is based on the logic of calculating the analgesia/nociception index proposed by a group of French researchers in 2006 [6, 7]. The normalized numerical index can be calculated in real time.

The aim of this study is to demonstrate, using the example of sports, the possibility of objective numerical monitoring of allostatic load, and to compare the methods of assessing AL by the latent time of the thermonociceptive response (LTTR) and heart rate variability.

1. Methodology

1.1. Theoretical background of the method. The proposed simple idea of standardization of load assessment became a logical integration of the following well-known provisions.

1. In 1991, Droste noted that an antinociceptive effect occurs after physical exercise of any kind [8]. Studies in humans and animals «have shown that physical exercise leads to temporary hypoalgesia. Reduced sensitivity to pain is not only demonstrable after long-distance exercise (e.g., marathon running), but also during and after intense physical exercise. Hypoalgesia persists after the exercise has stopped. This demonstrates that the systemic analgesic effect is caused by the exercise process» [8].
2. This effect of exercise can be explained by the activation of the endogenous opioid system (EOS) in response to their stress-inducing action, since opioids have analgesic properties. The three-component stress theory of S. B. Parin [9] positions the EOS as a stress-limiting system that limits the activation of the sympathoadrenal and hypothalamic-pituitary-adrenal systems. The EOS is present at all three stages of the stress reaction with varying degrees of dominance.
3. Clinical observations and experimental studies have shown a relationship between the concentration of endogenous opioid peptides in the brain, cerebrospinal fluid, blood plasma, the level of pain sensitivity and the origin of pain syndrome (Kaluzhnyi L.V.; Puzin M.N., Vyazmin A.Ya.) [10, 11]. "The pain threshold is not an absolutely stable value, but is subject to functional fluctuations that correlate with the content of opioid peptides...". It was proposed to evaluate the threshold of thermonociceptive reaction by a time interval and study its dynamics as one of the EOS state markers (Litvinova S.V., Nadezhdin A.V.) [12, 13].
4. Regulation of the heart rhythm is carried out by the autonomic nervous system (ANS) and humoral-metabolic influences. The ANS is under the modulating influence of the central nervous system and impulses arising in response to irritation of various intero- and

exteroceptors (reflex regulation). In the spectral analysis of the CIG, it is customary to distinguish frequency ranges: very low — VLF (0.003...0.040 Hz), low — LF (0.04...0.15 Hz) and high — HF (0.15...0.4 Hz) [2,3]. LF corresponds to sympathetic, HF — parasympathetic influences. The influence of the parasympathetic nervous system causes changes in the heart rhythm with a frequency of 0.15...0.5 Hz, forming the so-called fast or respiratory high-frequency waves (HF) [2, 3].

5. Since 2006, the Analgesia/Nociception Index (ANI) has been introduced into intraoperative practice, in which the degree of analgesia against the background of sedation is assessed by the respiratory effect on HRV [6, 7, 14–17]. It is claimed that the index does not depend on the heart rate and respiratory rate. The index shows the quality of anesthesia in conditions of the patient's lack of response due to sedation.

The antinociceptive effect that occurs during physical exercise can be explained by the activation of the EOS. Such activation was confirmed by the author by naloxone blockade of opioid receptors [18]. As a stress-limiting EOS, it is activated in parallel with a stressor, for example, physical exercise. The method for assessing physical activity proposed by the author is based on measuring its antinociceptive effect. The pain threshold after exercises of various directions is assessed by LTTR. Its dynamics are compared with the change in the respiratory effect on HRV, assessed by the index obtained in accordance with the ANI logic.

Since "the structure of the subjective sensory space is specific for stress, sympathotonia and vagotonia" [19], with insufficient counteraction of the EOS, the stress level remains high, which affects the subjective sensation of pain. The stress index (SI) is included in the pool of standard HRV parameters [2–4]. The index of tension of regulatory systems, the stress index is an indicator of variational pulsometry, characterizing the state of the central regulatory circuit. Resistant to episodes of rhythm disturbances, conductivity and recording artifacts. $SI = AMo/2M(x) \cdot Mo$, where $M(x)$ — mathematical expectation, Mo — mode, AMo — mode amplitude.

1.2. Data sources and study population. The data were collected using a cardio belt and a pocket battery-powered hand warmer routinely used in the training process. The study group consisted of four 1st-category orienteering athletes with a sympathicotonic type of vegetative regulation, aged fifteen: two girls (sports experience of 2 and 6 years) and two boys (experience of 2 and 6 years) without bad habits and chronic diseases. The data were collected during a three-day training microcycle of 4 sessions. Running loads performed: 9 km, (5×580 m), (2×1000 m), 15 km (girls) / 20 km (boys).

1.3. Registration of CIG. Cardiointervalogram (Fig. 1) — change in the interval between the R waves of the electrocardiogram over time — was recorded using a chest belt — a fitness heart rate sensor connected to a smartphone, with an accuracy of measuring cardiointervals of 1 ms [20].

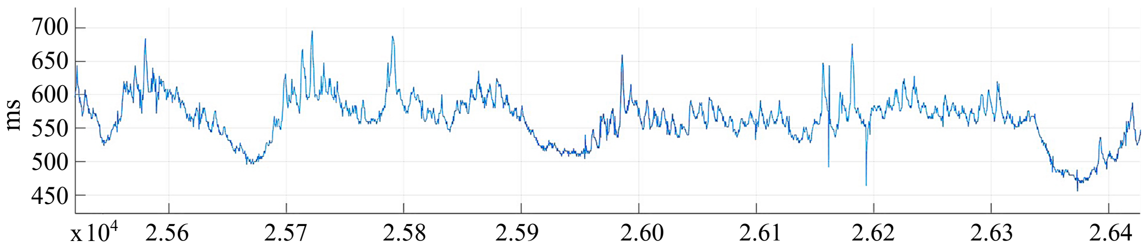

Fig 1. A segment of the original cardiointervalogram $\{RR\}$ with a duration of 19 minutes ($9 \cdot 10^2$ counts) and artifacts. Ordinate — value of the RR interval in ms, abscissa — number of the interval from the beginning of recording

1.4. Measurement of thermonociceptive response threshold. The pain threshold was assessed by recording the latent time of the thermonociceptive reaction. The measurement was performed in a sitting position in a separate room with the exclusion of distracting factors. The CIG was recorded in parallel.

The usual power and temperature of the hand warmer were reduced and stabilized to 5 W and 47°C. The athletes were asked to hold the warmer not with their full hand, as usual, but to place the wrist of the left hand at the base of the thumb on a 1×2 cm thermal plate. The holding time was recorded in seconds until discomfort appeared. LTTR measurements were performed before and 20–25 minutes after each training session.

The method was previously tested by the author when conducting a group statistical analysis of changes in LTTR in adult volunteers during long-term aerobic exercise [20]. Two significantly different samples were obtained — before and after the load (nonparametric Wilcoxon test for dependent samples, $p < 0.05$, number of participants 11). LTTR increased by 5.4 ± 4.2 times (Fig. 2). The group included participants with different qualifications, gender, EOS state, and ANS type.

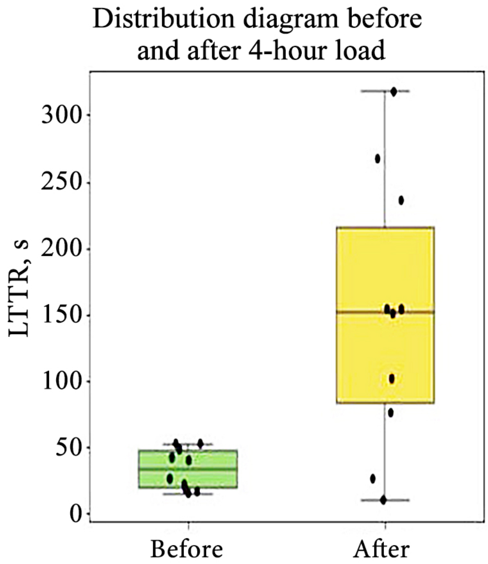

Fig 2. LTTR distribution diagram before and after long-term (> 4 hour) aerobic exercise. Standard deviation

1.5. Algorithm for normalization of the CIG. To measure the respiratory influence on HRV, transformations corresponding to the logic of the graphical measurement of the ANI index described by R. Logier et al. [6] are applied to the original cardiointervalogram RR. The respiratory pattern of HRV is present in the frequency range 0.15...0.5 Hz. The task: to obtain normalized HRV power in this range.

1. For the original time sequence of RR-intervals, by definition discretized non-uniformly, resampling and cubic interpolation of the CIG are performed at a frequency of 16 Hz. A new, uniformly discretized sequence $\{RR_N\}$ is obtained.
2. Gaussian smoothing is applied to $\{RR_N\}$ by computing a convolution with a Gaussian window G:

$$G(n) = \exp\left(-\frac{2(n - m/2)^2}{(am)^2}\right). \quad (1)$$

It has a size of $m = 256$ samples and a standard deviation of $a = 2$.

$$\{RR_M\} = \{RR_N\} * G / \sum G, \tag{2}$$

$\{RR_M\}$ — smoothed sequence.

Gaussian smoothing as a low-pass filter is better than moving average due to less spectral leakage.

3. By subtracting the smoothed sequence, $\{RR_N\}$ is decomposed into fast and slow components. $\{RR_F\} = \{RR_N\} - \{RR_M\}$, where $\{RR_F\}$ is the fast component of variability [21].
4. The sliding norm $\{S\}$ is calculated over a window of $m = 128$ samples $\{RR_F\}$.

$$S_i = 3 \cdot \sqrt{\frac{\sum_{j=1}^{m} (RR_{Fj})^2}{m}}. \tag{3}$$

5. Each element of the sequence $\{RR_F\}$ is divisible by the corresponding norm from $\{S\}$: $RR_{Fi} = RR_{Fi}/S_i$.
6. Since the method is based on measuring the amplitudes of the respiratory pattern HRV, we are interested in frequencies in the range of 0.15...0.5 Hz. This range is obtained by digital wavelet filtering with the Daubechies 4 basis wavelet from the fast component $\{RR_F\}$. When the sequence is restored after the wavelet decomposition, only the 4th and 5th decomposition coefficients remain, which corresponds to the range of 0.16...0.67 Hz. This is how the filtered $\{RR_{FF}\}$ [7] is obtained.
7. On the graph of the normalized sequence $\{RR_{FF}\}$, local negative minima and local positive maxima are located and connected to each other (Fig. 3). Changes in the area between the curves of local minima and maxima reflect changes in the cardiorespiratory interaction. The area is measured in normalized units.
8. On a segment with a duration of 512 samples (32 s), the horizontal axis is evenly divided into 4 parts (Fig. 3). The minimum area of 4 segments, $S_{\min}$, is determined. The instantaneous value $S_{\min}$ is calculated every 4 s, the moving average every 16 s, and the average S_{aver} for the period of interest, for example, for the time the hand is held on the thermal plate.
9. IRI is introduced — the index of respiratory influence on HRV, calculated as the percentage of filling the area between the field envelopes within the boundaries of ±0.1 n.u.

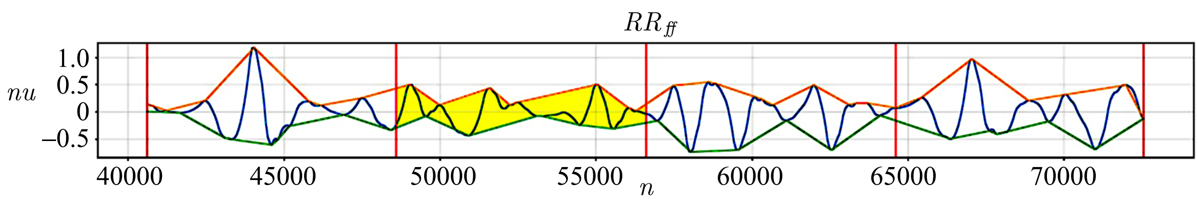

Fig 3. A segment of 512 samples of the normalized $\{RR_{FF}\}$. A quarter of the window with the minimum area between the extremum curves is filled in (color online)

2. Results

In Fig. 4 shows the change in LTTR in the microcycle classes of the group members.

The beginning and end of the segments correspond to the beginning and end of one session. The end of the second session is noteworthy. Based on the external signs of fatigue of athlete w2,

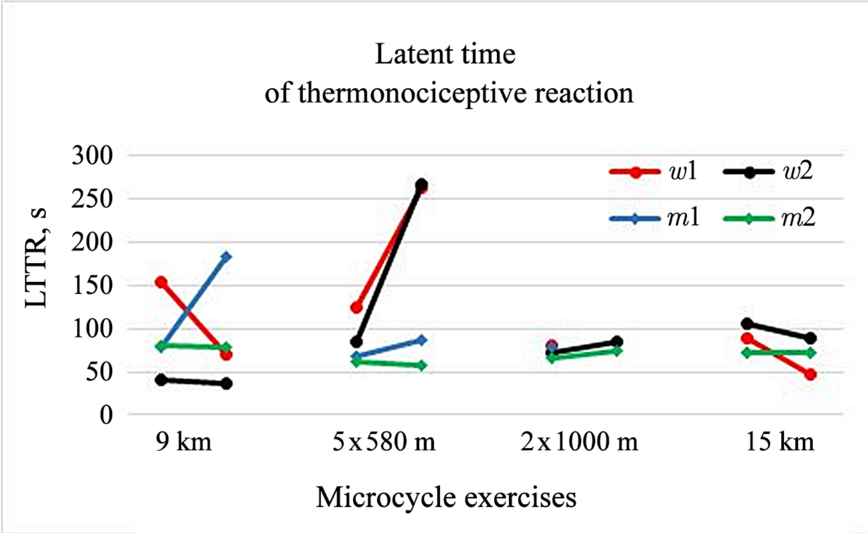

Fig 4. Changing the LTTR when performing four different exercises of the training microcycle for a group of athletes. One segment corresponds to one activity of the one person (w — girls, m — young men) (color online)

the coach reduced the task for her from 5 to 3 repetitions. In terms of physiological effect, this corresponded to a 5-fold repetition of participant w1 and was confirmed by LTTR measurements and IRI calculation (see the end of the second segment in Fig. 4 and column 4 in Fig. 5). We see that young men m1 and m2 tolerated this load easier. At the same time, as Fig. 4 shows, at the first training session 9 km were harder for participant m1 than the others, which corresponded to a more intense passage of the distance. For athlete w1, the session was of a restorative nature. Obviously, the dynamics of LTTR allows tracking the allostatic load of the activity.

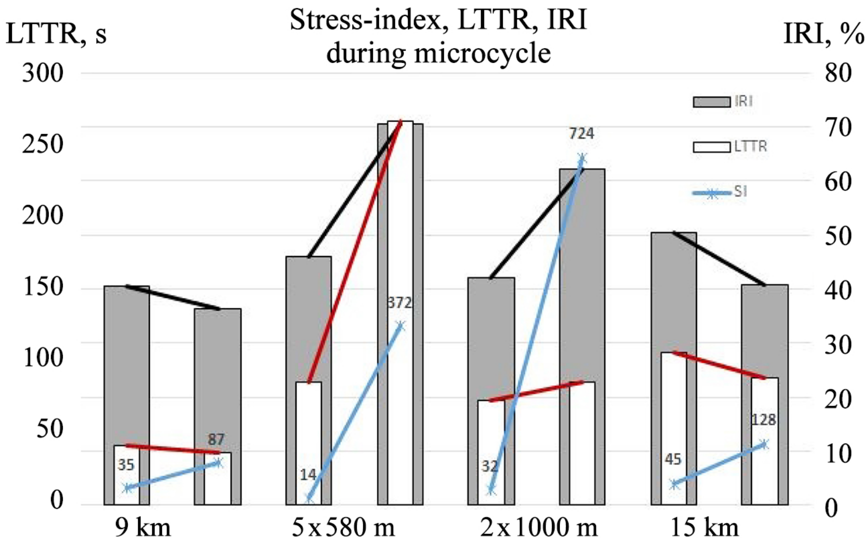

Fig 5. The hanges in the training microcycle of the athlete w2: LTTR (s) — the white columns, the latent time of the thermonociceptive reaction; IRI (%) — the gray columns, the index of the respiratory effect on HRV. For clarity, red and black lines connect the states before and after training. The segments with numbers show the value of the stress-index SI (color online)

To demonstrate the possible correlation of individual physiological parameters, Fig. 5 shows the results obtained for athlete w2 (sports experience of 6 years). Participant w2 was chosen due to the greatest completeness of the registered experimental data. The figure shows a high correlation between the level of thermonociceptive sensitivity estimated by LTTR and the normalized high-frequency power of HRV in the range of 0.16...0.67 Hz (index IRI). Its numerical estimate shows the value $r = 0.86$.

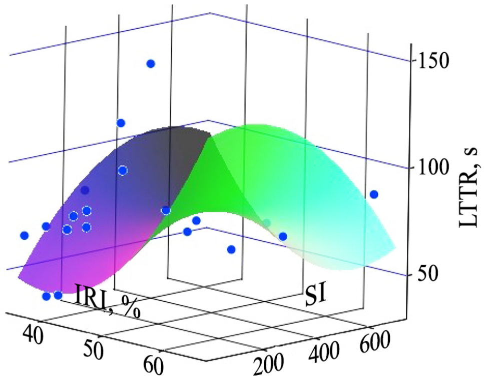

Fig 6. The surface of quadratic two-factor regression $f(IRI, SI)$ (color online)

The equality of the LTTR in columns 3 and 6 of Fig. 5, despite the differences in the IRI level, is associated with different stress levels. Stress uncompensated by the EOS can disrupt the correlation in the data of other athletes. For other participants, the coefficient value is not given due to the obvious incompleteness of the experimental data.

By introducing an additional stress factor SI, the presented small-volume data (4 athletes and 4 episodes of physical activity) can be described by a quadratic mathematical model (Fig. 6).

$$f(IRI, SI) = C_0 + C_1 \cdot IRI + C_2 \cdot SI + C_3 \cdot IRI \cdot SI + C_4 \cdot IRI^2 + C_5 \cdot SI^2, \quad (4)$$

where $f(IRI, SI)$ is the latent time of the thermonociceptive reaction, $C_0...C_5$ are the coefficients describing both the independent and synergistic influence of the factors IRI and SI. The Table presents the values of the two-factor regression coefficients obtained by the least squares method.

The analysis showed that IRI and SI influence independently and mutual reinforcement is insignificant.

The proposed model potentially allows replacing the labor-intensive procedure of measuring LTTR with the calculation of IRI and SI indices in real time and eliminating the subjectivity inherent in LTTR.

Table

C_0	C_1	C_2	C_3	C_4	C_5
-299.764	13.688	0.066	$-5.355 \cdot 10^{-3}$	-0.107	$2.528 \cdot 10^{-4}$

Conclusion

The work shows that the dynamics of LTTR allows tracking the allostatic load of activity. LTTR allows assessing the degree of physiological analgesia that occurs as a result of the load on the body.

It is also shown how the inconvenient, subjective procedure of LTTR measuring that takes participants out of the context of an action can be replaced by an objective, unmanipulable analysis of heart rate variability. A model is proposed that links LTTR as an assessment of AL with the respiratory influence index IRI and the stress index SI.

The original graphical calculation of the normalized HRV power in the range of 0.16...0.67 Hz (IRI) [7] allows to bypass nonlinear interactions of regulatory systems, which are paid attention to in the traditional approach to HRV analysis [1–5]. It does not depend on episodic rhythm and conduction disturbances, is not sensitive to recording artifacts, and does not depend on respiratory rate and heart rate.

The proposed approach demonstrates the presence of reference values in the studied group, but requires further specially planned clinical studies of statistically significant groups to confirm the objectivity and reproducibility of the proposed method.

It is expected that a publicly available mobile application will help to adequately assess the current allostatic load in real time during any type of activity.

It is assumed that the study of the dynamics of instantaneous IRI and SI values can help in assessing the speed of deployment and the effectiveness of the EOS as a stress-limiting system.

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