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Polishchuk S.V.THE METHODOLOGY OF ASSESSING THE EFFECTIVENESS  
OF THE THERAPY

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**Abstract**

**Objectives:** To substantiate the methodology for assessing the effectiveness of drug therapy, based on the effect of therapy not only on the target organ or function, but also on the regulatory and adaptive status (RAS) of the organism.

**Material and methods:** The cardio-respiratory synchronism test (CRS), proposed as one of the rationale for the concept of the hierarchical system of cardiac rhythmogenesis in an integral organism, was used to evaluate the RAS, since it characterizes the complex reaction of the two most important vegetative functions – respiratory and cardiac. The technique of obtaining cardio-respiratory synchronism in humans, analyzing its parameters and calculating the regulatory-adaptive status index (iRAS) by the parameters of the CRS is described.

**Results:** Pronounced changes in iRAS under cyclic changes in the body of pregnant women with psycho-emotional stress before delivery are shown expressed. These observations revealed high information value of the method in assessing the dynamics of regulatory and adaptive capabilities of the organism. Monotherapy of arterial hypertension was carried out by agents of different groups. The treatment outcomes were compared in those patients who reached the target blood pressure level in 6 months (140/90 mm Hg). It was found that under the same effectiveness of therapy according to the target function parameter – the level of blood pressure, preparations of different groups had unequal influence on the body's RAS. In the treatment with lisinopril, hydrochlorothiazide, nifedipine, and diltiazem, iRAS increased; when treated with atenolol and doxazosin, on the contrary, it decreased below the baseline values before the start of the therapy.

**Conclusion:** The evaluation of the dynamics of RAS provides a new methodological approach to the characterization of the effectiveness of drug therapy, based on the assessment of the effect not only on the target organ or function, but also on the regulatory and adaptive capabilities of the organism.

**Key words:** cardio-respiratory synchronism; regulatory-adaptive status; quantitative assessment of regulatory-adaptive possibilities of the organism; drug therapy; assessment of the effectiveness of drug therapy.

**Introduction**

It is made to evaluate the effectiveness of drug therapy on the effectiveness of its influence on organ or duty of the target; for example, normalization of blood pressure in the treatment of hypertension, the degree of reduction of myocardial remodeling in chronic heart failure, etc. This approach doesn't consider the most important component – the influence of treatment on the general condition of the body and first of all on the regulatory-adaptive capacities that determine the quality of human life. This is because until recently there was no method for objective quantitative assessment of regulatory-adaptive status (RAS) in the body. The last became

possible with the introduction of the method of rating RACES by means of cardio-respiratory synchronism (CRS) and analyzing its parameters.

**Method of research**

*1. Cardio-respiratory synchronism – the model of rhythm played by heart.*

The phenomenon of vegasno-cardiac synchronization, lied in the fact under the volley stimulation of the vagus nerve there was observed the synchronization of the rhythm of vagus nerve stimulation with the rhythm of the heartbeat, has been studied in our laboratory for several years [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. The phenomenon occurs in animals with vagal innervation of the heart; it has

been studied in 10 animal species [11, 12]. The task was to determine the role and place of this phenomenon in the mechanisms of heart rhythm in the whole ("intact") human and animal's body. It resulted in the creation of the model where the rhythm of signals generated in the brain travels to the heart via the vagus nerves and triggers the rhythm of heartbeats synchronous with it. We saw the way to create such a model in a close relationship of cardiac and respiratory rhythmogenesis. This relationship is well known and has been studied in a large number of studies [13-20]. Key center of this interaction is the medulla oblongata. It is shown that the same interneuron in the field of the nuclei of the vagal complex of the medulla oblongata shows the switching activity now in the rhythm of the breath, then in the rhythm of heartbeats. During inhalation, its activity is synchronous with contractions of the diaphragm, and while exhaling it is synchronous with the contractions of the heart [21]. Fundamentally important is the fact that breathing is the only autonomic function that has an "arbitrary control": a person can consciously change the rate and depth of respiration [22]. It allowed us to offer that the way of creation of the same synchronous rhythm of breathing and of the heart with human by reproducing a predetermined frequency of arbitrary breathing that is usually above the initial cardiac rhythm is cardio – respiratory synchronism (CRS).

The rhythm of signals coming via vagus nerves to the heart and leading to synchronization of the rhythm of heartbeat and breathing, probably caused by the involvement of the cardiac efferent neurons of the medulla oblongata in the dominant frequency of the respiratory rhythm.

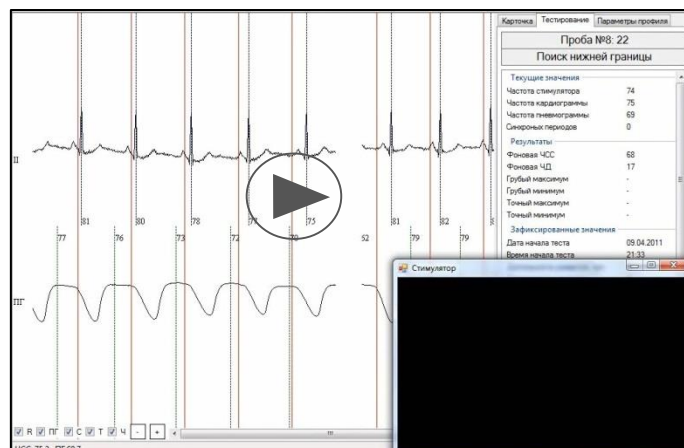
The fact of receipt to the heart of signals along the vagus nerves to the rhythm of the breath when CRS was analyzed in experiments on dogs when placing animals in a thermal insulating chamber. Under these conditions the animals received tachypnea, against which manifested CRS. The transaction of preliminarily bred vagus nerves under the skin of the neck stopped the synchronization of cardiac and respiratory rhythms. The heart rate and respiration remained high, but were not synchronous. As a result of these experiments, it was shown that the signals that lead to synchronization of cardiac rhythm with breathing came by the vagus nerves [23].

## 2. Techniques for cardio-respiratory synchronism in humans

As far as we were studying the phenomenon of CRS, the technique of its receipt was improved and currently there is a software-hardware complex in automatic mode [24] that represents the following algorithm.

After the registration of the initial electrocardiogram (ECG) tracing and pneumogram (PG) the trial subject is invited to breath in time to signal appearing on the screen of the monitor. Signals go with a certain frequency, which varies by a program as described below. The research process of CRS consists of a series of samples (with each sample, the trial subject is invited to reproduce a given breathing frequency). The aim of each trial is to establish the existence of synchronization of rhythms of arbitrary rapid breathing and heartbeat on given frequencies. The fact of the presence of CRS is set by automatic measurement of intervals R-R on ECG, the distance between the identical elements on PG and marks of the signalling that sets the rhythm of the breath. If the listed parameters are equal between themselves, the presence of CRS at a given frequency is reported (Video 1).

The first sample is set to the frequency of signals for 5% below the initial cardiac rhythm. After the recovery the heart rate and respiration rate at the initial level starts the next sample. Samples are held with a 5% increase in the frequency signals in each successive sample. The program notes set of the frequency of breathing when the first successful trial (the presence of synchronization) and continues increasing frequency signals with the same 5% increments from the previous value. This increase on each subsequent trial is continued as long as the patient reproducing every time a new set rhythm of breathing, doesn't stop the development of CRS. The final stage of the analysis is to define the frequency of the first and the last scoring trial, i.e. the trial, when first CRS was developed and the one when it was lost. To clarify the first productive sample the signal frequency set at 2-3% below the effective value. If the result is negative, the required value remains the same. If the result is positive and the CRS is formed, the frequency is again reduced with 2-3% step until CRS stops to develop. Clarification of the last successful frequency is carried out in a similar way, but with a 2-3% increase in frequency.



**Video 1.** Measurement of the sample of cardio-respiratory synchronism in humans

In the study of CRS are recorded the following parameters:

- 1) initial heart rate (HR) and respiratory rate (RR);
- 2) the minimum limit of the range of timing – the frequency of the respiration, when the first CRS was identified;
- 3) the maximum limit of the synchronization range – respiration rate at the last test with fixation of the CRS;
- 4) the synchronization range is the difference between the maximum and minimum limits;
- 5) the duration of the process of synchronization development on the minimum of the range is the number of cardiocycles from the beginning of the sample to the first synchronous breathing cardiac

cycle at the minimum barrier of the range of synchronization;

- 6) the developmental period of the synchronization at the maximum barrier of the range is the number of cardiocycles from the beginning of the sample to the first synchronous breathing cardiac cycle at the maximum barrier of the range of synchronization;
- 7) the difference between the initial heart rate and the minimum limit of the range of synchronization;
- 8) the duration of recovery of heart rate after the synchronization on minimum and maximum limits.

The parameters of CRS are estimated quantitatively, their dimensions and designation are presented in table 1.

Table 1

**Parameters of cardio-respiratory synchronism**

Options	Dimension	Brief designation
The original heart rate	hr/minutes	Orig. HR
The original respiratory rate	rr/minutes	Orog. RR
The minimum limit of the range of timing	srcr / minutes	Min Ran.
The maximum limit of the synchronization range	srcr / minutes	Max Ran.
The synchronization range	srcr / minutes	SynRan
The developmental period of the synchronization at the minimum barrier of the range	cc	DevPer Min Ran.
The developmental period of the synchronization at the maximum barrier of the range	cc	DevPer Max Ran.
The duration of recovery of initial heart rate after the termination of the sample and the minimum barrier	cc	RecovPer Min Ran
The duration of recovery of initial heart rate after the termination of the sample at maximum barrier	cc	RecovPer Max Ran
The difference between the minimum barrier of the range of synchronization and initial heart rate	cc / minutes	Diff betw Orig. HR and Min Ran

Note: cc – cardiocycle, srcr – synchronous cardio-respiratory cycles

*3. Cardio-respiratory synchronism – a new approach to the assessment of regulatory-adaptive possibilities of organism*

The sequence of the processes developing in the implementation of CRS can be represented by the following stages: perception of the signal to set the respiratory rate, the processing and evaluation of this signal, the formation of the problem of arbitrary control respiration, reproduction respiratory rate in exact accordance with the frequency of the applied signal, the interaction of the respiratory and cardiac centers of the medulla oblongata, the synchronization of rhythms of breathing and heart centers, transmission of efferent signals to the heart along the vagus nerves, the interaction of the signals came along by the vagus nerves from the rhythmogenic structures of the heart, playing by heart frequency of these signals is the development of CRS.

In the development of SDS a multi-level system of structures and mechanisms that ensure the formation and implementation of the control signal are involved. The last opens up the unique possibility of using CrS for integrative assessment of the state of regulatory systems of the body. In the implementation of the process of adaptation as regulatory influences and the impact of the disease, the key role is played by the complex reaction of the vegetative provision. The fundamental difference between the proposed methodological approach to the assessment of regulatory-adaptive possibilities of the method of CRS, was the usage of the reaction of the two major autonomic functions – breathing and heart in their interactions. CRS allows the quantitative assessment of regulatory-adaptive status (RAS) of the human body.

It is crucial to select those changes which increasingly characterize RACES of the organism from a set of parameters of CRS. The result of many years of multidisciplinary research [25, 26, 27, 28, 29, 30] revealed that the most important parameters are the range of timing and duration of development synchronization at the minimum barrier of the range.

In states characterized by deterioration of the regulatory-adaptive processes (stress, disease) occur reducing the range and increasing in time of the development of synchronization at the minimum barrier. The greater the degree of deterioration of adaptive capacity, the more pronounced decreases range and increases significantly the developmental period of the synchronization on the minimum border. In States characterized by deterioration of the regulatory-adaptive processes (stress, disease) occur

reducing the range and increasing the time development synchronization at the minimum limit. The greater the degree of deterioration of adaptive capacity, the more pronounced decreases range and significantly increases the duration of the developmental period of the synchronization on the minimum barrier.

In order to integrate two the most informative parameters of CRS, reflecting the RACES, it was asked to think of their relationship expressed by the formula:

$$IRAs = (SynRan / DevPer Min Ran.) \times 100.$$

For the qualitative assessment of the level RAS, the scale was proposed (table 2).

Table 2

**Scale of qualitative evaluation of the level of regulatory-adaptive status depending on the value of the index (IRAs)**

Regulatory-adaptive status	IRAs
<b>Hight</b>	more than 100
<b>Well</b>	99-50
<b>Satisfying</b>	49-25
<b>Low</b>	24-10
<b>Unsatisfying</b>	1-9

Thus, determination of RACES by the method of CRS is fundamentally different from earlier used approaches based on the estimation of the reaction of any autonomic functions. Quantitative characterization of complex reactions of the two major autonomic functions enables us to characterize the response of the body as a whole system.

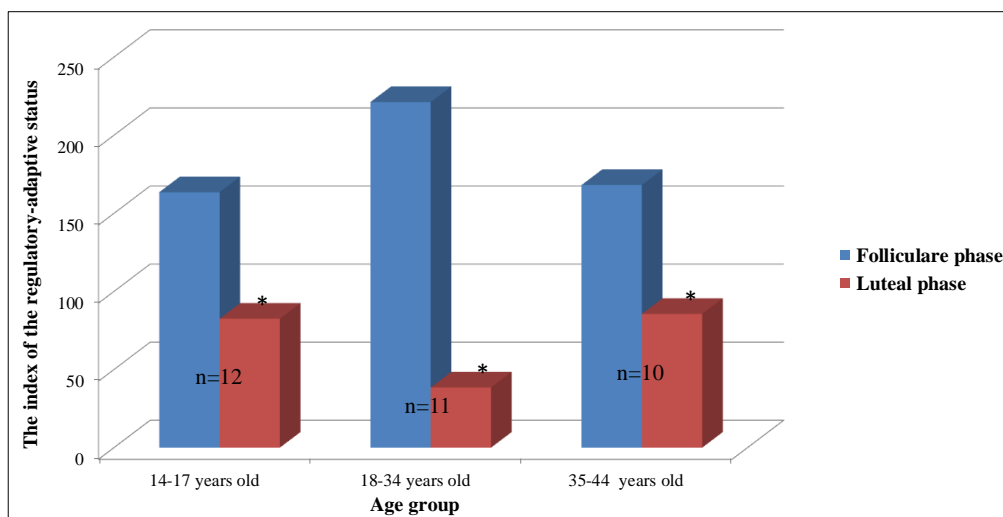
**Results**

*4. Regulatory-adaptive status in certain functional states of the organism.*

*4.1. Regulatory-adaptive status under the cyclic changes in the female body*

i) The observations were performed on women of reproductive age with the duration of the menstrual cycle is 28-32 days. Women were divided into 3 groups according to age: 14-17 years 18-34 years, 35-44 years. CRS method assessed races in the follicular and luteal phases of the menstrual cycle [31]. Dynamics of values of the IRAs is shown in figure 1.





**Fig. 1.** The index of the regulatory-adaptive status of women with the duration of the menstrual cycle is 28-32 days in different age groups depending on the phase of the cycle ( $m \pm m$ ). \* – the accuracy in comparing values in different phases for each age group is  $p < 0.001$

In all age groups there was a decrease of IRAs in the luteal (second) phase of the menstrual cycle in relation to the value of IRAs in the follicular (first) phase.

The increase in IRAs in the follicular phase indicates an improvement of the regulatory-adaptive possibilities of the organism. It is accompanied by an increased lability of the Central nervous system, that was confirmed by the increase in the critical frequency of flicker of the bulb, reducing the time of the conditioned reflex to light and sound in the follicular phase of the menstrual cycle.

Along with changes to IRAs it was also noted the passability dynamics of the level of sex hormones: the more the ratio between estradiol and progesterone due to the increase in estradiol in follicular phase, the more IRAs. In the luteal phase of a change in the relationship between steroid hormones increase progesterone is associated with a decrease in the IRAs. in more detail the described the changes of RACES in the phase of the menstrual cycle are expressed in the age group of 18-34 years.

#### 4.3 Regulatory-adaptive status of pregnant women before the childbirth

Childbirth is a reflex act, arising due to the interaction of body systems of the mother and fetus. Births occur in the presence of generic dominant, the formation of which has a value the effects of sex hormones on various formations of the central and peripheral nervous system. The need for objective, integrative assessment of the readiness of the female body for childbirth is obvious.

The study included healthy pregnant women (aged 20 to 39 years) in pregnancy from 37 to 40 weeks, with namoxicillin the fetus.

Before the beginning of the childbirth the surveyed was conducted to evaluate the readiness of the body for childbirth twice (1 time in 5 days) by the conventional clinical criteria: the maturity of the cervix, and oxytocin, colpocytologic tests. At the same time in the same period RACES were evaluated. At the moment of the survey 47 women had 37 weeks of pregnancy, 41 had 38 weeks and 34 in the period of 39 weeks. Within 1-2 days after the second survey the birth occurred [32].

In the prenatal period of pregnant women, childbirth is physiologically proceeded ( $n=34$ ), the closer the date of birth IRAs was increased.

The pregnant women who gave birth physiologically on 38<sup>th</sup> week of gestation, IRAs of 37 weeks was  $52.5 \pm 3.7$ , while IRAs in 38 weeks was equal to  $109.0 \pm 5.4$ .

In pregnant women who gave birth physiologically on 39<sup>th</sup> week of gestation IRAs of 38 weeks was  $85.3 \pm 4.5$  and IRAs of 39 weeks was  $125.0 \pm 8.7$ .

In the prenatal period in pregnant women who gave birth physiologically on 40<sup>th</sup> week of gestation, IRAs of 39 weeks was equal to  $89.5 \pm 1.15$ , and of 40 weeks was  $145.2 \pm 12.5$ .

The presented the dynamics of the IRAs demonstrates that pregnant women have an increase in RACES as approaching to childbirth.

The values of IRAs in women during the last week before childbirth, be it 38, 39 or 40 week presents epy high-level RACES. This indicates that the body at this time has reached the functionality that we needs at birth. Rating RACES gave an opportunity to objectively ascertain the result of such

a complex process as the mobilization of the female body before birth.

The fact that all women of analyzed groups of pregnancy ended with a physiological childbirth, birth of fetuses with Apgar score 8-10 points, allows to use the obtained dynamics of the IRAs in the prenatal period as a test of an estimation of readiness of an organism for childbirth.

Pregnant women at the time 38-40 weeks of gestation, childbirth was complicated by the discoordination of childbirth activity and was completed by caesarean section (n=22) [33], 1-2 days before birth, IRAs decreased from 33.2±0.9 to 21.7±0.51 (gave birth at 38 weeks), from 28.3±1.0 to 17.5±0.45 (gave birth at 39 weeks), from 25.0±1.15 to 7.8±0.3 (gave birth at 40 weeks). Pregnant at the time 38-40 weeks of gestation, childbirth was complicated by the primary weakness of childbirth activity and ended with the operation cesarean section (n=21), IRAs dropped to 0. Pregnant women, whose childbirth was complicated by the discoordination of childbirth or primary uterine inertia, IRAs pointed to the cost advantages of the body. Therefore, the dynamics of IRAs gives the ability to predict the development of complications at birth and to predict the effectiveness of their therapy.

*4.3. Regulatory-adaptive status with psycho-emotional stress*

Studying the functional state of organism on the

background of stress was revealed a significant deterioration of the regulatory-adaptive possibilities. As a stress factor the direction of patients with large-volume education in the breast Oncology center for diagnosis was made [34].

The regulatory-adaptive status was evaluated at 218 women with voluminous formation in the mammary gland in the primary treatment for a cancer doctor. IRAs on the background of the stress associated with anxiety for the result of verification of diagnosis was 32.1± 1.47.

Re-evaluation of the regulatory-adaptive status of women in the non-confirmation of the cancer diagnosis showed a significant increase in IRAs, it was 87.1±6,0, that shows an increase in RACES after the removal of stress.

Women with a confirmed cancer diagnosis had a further decrease of IRAs compared to a study in circulation and it was equal to 21.3±1.7 that clearly demonstrates a negative effect on RACES exacerbating of a stressful situation. Thus, IRAs is a reliable indicator of the state of the organism under stress.

It was investigated the influence of personality type on the degree of stress response [35]. 110 women at the first visit to the oncologist were determined the type of temperament. The results of the evaluation of RAS patients based on the type of temperament (p<0.001) presented in table 3.

Table 3

**The index of the regulatory-adaptive status (IRAs) of women with different temperament types on the first appeal, confirmation or denial of the cancer diagnosis (M±M)**

<b>The conditions of determining IRAs Personality type</b>	<b>The first treatment to the Oncology dispensary</b>	<b>Upon the disconfirmation of cancer diagnosis</b>	<b>Upon the confirmation of cancer diagnosis</b>
Phlegmatic (n=11)	66.5±2.9	138.2±4.7	24.7±1.3
Sanguine (n=24)	47.7±1.6	113.4±2.4	20.3±1.3
Melancholic (n=32)	34.9±0.45	85.8±3.3	12.5±1.7
Choleric (n=33)	31.1±0.3	71.1±1.7	9.1±0.7

The data showed a greater degree of influence of the type of temperament on the RACES under the influence of stress. Thus, the most adapted to this situation was the phlegmatic and the least was choleric.

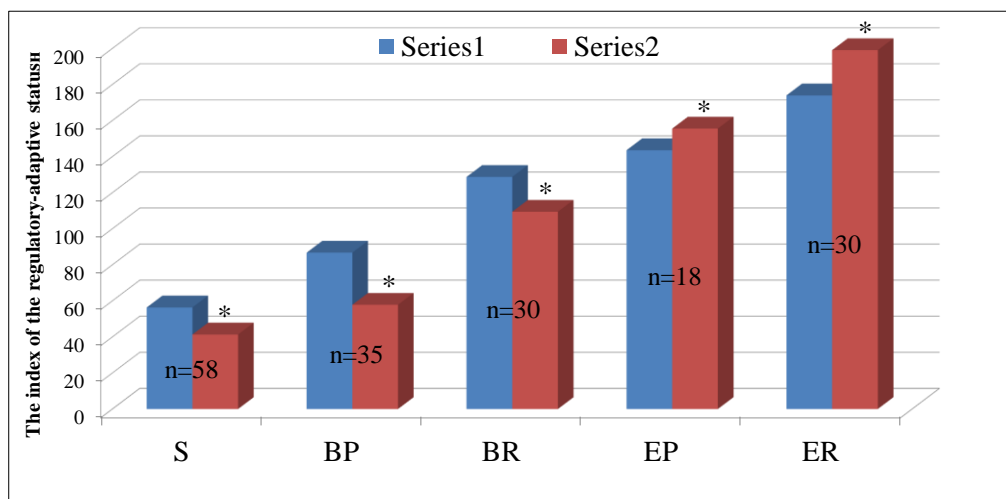
Thus, genetically predetermined the different degree of response of the organism to the same degree of stress, in this connection a question was raised about objective characteristics of such qualities as stress resistance using the method of CRS.

*4.4. Regulatory-adaptive status in the assessment of stress resistance*

Based on the study of IRAs a new quantitative method of determining the stress resistance of the person evaluating the dynamics of the RACES of the organism under the influence of stress load was developed [36]. Methodology of the study is to measure the IRAs before and after the test, to simulate the stress with the subsequent interpretation of the results in the following algorithm. People having under the action of stress factors of RAS,

expressed by the value of IRAs, unchanged or declined by no more than 5-6% of the original value, constitute a group with a high level of stress. Subjects who have IRAs not reduced by more than 50% under the action of stress factors consist the group with a moderate level of stress. People who have IRAs exceeded 50% in response to the stress reduction, belong to the subjects with a low level of stress.

We tested the method on three models of stress: 1) examination; 2) the stress caused by the parachute jump; 3) stress caused by leaving the emergency zone. The observations were performed with the participation of 58 students, 53 parachutists and 60 rescuers. The dynamics of change in IRAs in each of these categories is shown in 0



**Fig. 2.** The index of the regulatory-adaptive status in the initial state and under the action of stress factors in students (S), the beginners parachutists (BP), beginner rescuers (BR), experienced parachutists (EP), experienced rescuers (ER); \*  $p < 0.001$

In all three models of stress was shown that the method is highly informative. Evaluation of stress tolerance on the dynamics of the RACES allows to objectively characterize the resistance of stress and may be included in a set of tests for the selection of people dedicated to work in difficult and extreme conditions.

It is important to note that experienced parachutists and rescuers stress factor caused an increase of the IRAs that demonstrate the role of training to the effects of extreme factors.

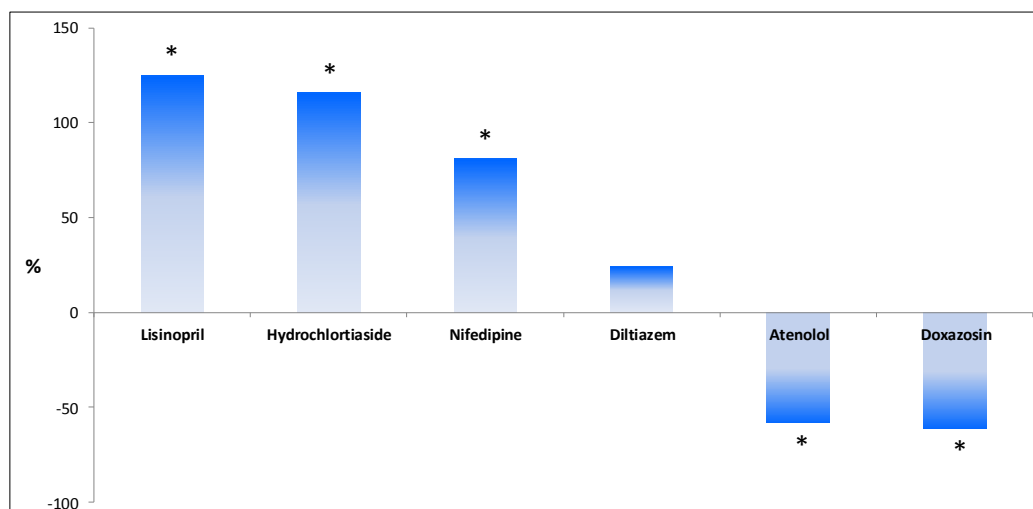
#### 4.5. Regulatory-adaptive status in the evaluation of the effectiveness of drug therapy

Considered method of evaluation of RAS opens up new possibilities to characterize the efficiency of drug therapy, allowing to determine not only the impact of the drug on the body or the function of a target, but changing the state of the body as a whole system under the influence of treatment.

The assessment of RACES was carried out to determine the effectiveness of drug therapy in the treatment of hypertension. Monotherapy of arterial hypertension was carried out by agents for 6 months – representatives of various groups: lisinopril (angiotensin-converting enzyme inhibitor) [37], hydrochlorotiaside (thiazide diuretic), nifedipine (a blocker of slow calcium channels of digidropiridin

series), diltiazem (a blocker of slow calcium channels of benzodiazepin range) [38], atenolol (beta-blocker) [37], doxazosin (alpha1-blocker) [39]. There were compared the results of treatment of patients who after 6 months achieved the target of BP level ( $<140/90$  mm Hg. calendar). It was found that under the same effectiveness of therapy according to the parameter of the function target – level blood pressure, drugs of different groups had a differential impact on RACES of the organism, which is presented in 0figure 3.

As can be seen from figure 3, lisinopril increased IRAs on 124.9%, hydrochlorotiaside on 116.1%, nifedipine to 81.4%. Diltiazem, by normalizing the AD slightly changed IRAs. Of particular interest is the study of blockers with neogneopasen effect on the heart rate. They cause the antihypertensive effect, affecting different target organs. Doxazosin – alpha-1-blocker with a strong vasodilatory effect, atenolol is a beta-blocker with negative chrono – and inotropic effect. Atenolol IRAs was reduced by 57.9%, doxazosin at 61.1 per cent. Such dynamics of IRAs in application of blockers indicates a decline in the RACES, although the target parameter is the target blood pressure has been achieved.



**Fig. 3.** The direction of change of the index of the regulatory-adaptive status in the treatment of antihypertensive drugs. The zero line – the initial level before treatment. \* – reliability in comparison with the initial level of  $p < 0.05$

Thus, the presented facts allow to put the question on a new approach to the assessment of the effectiveness of pharmacotherapy. Demonstrated that achievement of target blood pressure was not always accompanied by optimization of regulatory-adaptive possibilities of the patients. This dictates the need to assess not only the intended effects of drug treatment on the organs and parameters of the target, but also on the general condition of the body. This approach to evaluation of pharmacotherapy opens up new possibilities for personalizing the treatment optimization and prediction of diseases.

### Conclusion

The phenomenon of cardio-respiratory synchronism in the conscious reproduction of the human asked breathing frequency commensurate with the frequency of heartbeats, has been received as one of the most important components in the system of scientific facts supporting the hierarchical organization of rhythmogenesis of the heart in the whole (intact) organism [23, 40, 41]. A method of the assessment of regulatory-adaptive possibilities of an organism the basis of which was the phenomenon of the CRS, is characterized by sufficient simplicity of the reproduction, non-invasive, quantitative expression of the result and highly informative. Informativeness is due to a complex assessment of participation in regulatory-adaptive reactions of the two major autonomic functions of the body – the heart and respiratory in their interaction. These advantages led to the feasibility of using of the method to characterize the regulatory-adaptive possibilities of an organism in a wide range of functional states, a variety of changes in the internal environment of the body, with effects on physical and social factors.

This article presents the performance of the method to characterize RACES in certain functional states of a human, upon the exposing to the body psychoemotional stress and to evaluate the stress resistance of the organism. Such a high sensitivity of the method in the studied conditions has opened prospects for its use for an objective quantitative characteristics of the efficiency of different effects on the body. Assessment of regulatory-adaptive status of the human body allows us to propose a new methodological approach to the characterization of the effectiveness of various methods of treatment, especially medication, describing the effect of the therapy not only on the organ or function of the target, but also on the organism as a whole system. This will allow to re-evaluate the results of treatment, personalizing and improving it.

**Conflicts of Interest:** The authors have no conflict of interest to declare.

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