Natural strengthening of immunity

Physical exercise and naturopathy
Dear Reader!

Our life dictates what topical issues should be discussed by the current Journal issue. Our scientists are carefully analyzing the current situation in the world and trying to avoid snap findings. Time shows us possible ways of how to solve the complex health care problems. The key conclusion can be very simple: a human being must be healthy, and as a consequence, his/her immune system must be tuned to respond to unfavorable infection attacks in an optimal manner. Therefore we have asked some our researchers to voice their opinions how to strengthen the human immune system. We think it is useful for every of us and therefore publish their recommendations and statements on the first pages in this issue.

We should mention that Cardiometry is a fine diagnostics tool to assess heart life expectancy. Our experts, using Cardiocode in “red zones” in intensive care units, have confirmed effectiveness of non-invasive measuring of the hemodynamics data on the cardiovascular system performance in critical patients with different severity degrees. The medical staff involved had a possibility not only to monitor the state in each critical patient, but also to predict and control the progression of a disease. We are going to publish some results of this pilot study in our next issues.

We are optimistic about the future of Cardiometry and do believe that with developing telemedicine it can solve a great variety of most complicated practical problems. And our aim is: disease prevention and protection.

Sincerely yours,

Editorial Board
Cardiometry
The metabolism rationale for applying of succinate-based compositions to maintain high performance in a human organism
Eugene I. Maevsky, Anna A. Vasilieva, Elena V. Grishina, Mikhail L. Uchitel, Lyudmila A. Bogdanova, Mikhail V. Kozhurin
Our paper reflects basic principles, which are decisive for the design of the offered succinate-based agent to increase the organism performance and the rate of recovery after intensive physical loading. We have treated a special role of the metabolic conversions of succinate in energy exchange of mitochondria: high energy efficiency, possibility of beneficial oxidation under oxygen deprivation, anaerobic formation and possible consequences of the above phenomenon.

Cardio-oculometric indicators of psychophysiological readiness of students to examinations
Vladimir A. Zernov, Elena V. Lobanova, Elvira V. Likhacheva, Lyubov P. Nikolaeva, Diana D. Dymarchuk, Denis S. Yesenin, Nikita V. Mizin, Aleksandr S. Ognev, Mikhail Y. Rudenko, Natalia Y. Galoi, Anna R. Sudarikova
Cardio-oculometric indicators to grade psychophysiological readiness of students to examinations are described herein. Given is an experimental evidence that transitions from a low level of psychophysiological readiness of students to examinations to a high level of such readiness thereto is really accompanied by significant changes in the organism performance, first of all, in that of the heart.

The importance of the study of central hemodynamics using volumetric compression oscillometry in clinical practice: resolved and unresolved issues
Roman V. Gorenkov, Mikhail A. Yakushin, Diana E. Safina, Olga G. Dvorina, Sergey A. Orlov, Natalia P. Chernush
The article discusses the promising possibilities of using the method of volumetric compression oscillometry in clinical practice, which allows to simultaneously determining 20 indicators of central hemodynamics.

Cardiometric evidence data on human self-control of emotional states in the context of the use of metaphoric associative cards
Vladimir A. Zernov, Elena V. Lobanova, Elvira V. Likhacheva, Lyubov P. Nikolaeva, Diana D. Dymarchuk, Denis S. Yesenin, Nikita V. Mizin, Aleksandr S. Ognev, Mikhail Y. Rudenko, Natalia Y. Galoi, Anna R. Sudarikova
The paper presents our experimental evidence of validity of our hypothesis that definite, substantively different, psychophysiological states of a human individual can be really fixed with the use of metaphoric associative cards.

Assessment of system-related hemodynamics and tissue hydration in female patients with preeclampsia
Nikolay N. Chernov, Aleksandr A. Bezverkhii
Multifetal pregnancy is a risk factor for developing of preeclampsia. The given study has been designed to obtain main data measured in pregnant patients experiencing preeclampsia.

Signal morphological criteria for cardiotoxicity in breast cancer chemotherapy
Alia I. Shikhlyarova, Elena M. Frantsiyants, Lyubov Y. Vladimirova, Anna E. Storozhakova, Larisa N. Vashchenko, Emma E. Kechedzhieva, Galina V. Zhukova, Elena A. Sheyko
The toxogenic effect of anthracycline drugs on the cardiovascular system under conditions of oncological pathology determines the need to expand the diagnostic capabilities for detecting cardiotoxicity, including searching for signal morphological markers in blood serum.
The study of hemodynamics in critical patients under intensive care unit conditions
David M. Tamrazyan, Alla I. Shikhlyarova, Oleg N. Kopylov, Olga G. Pyagai

Studies of hemodynamics in critical patients under intensive care unit conditions have been a very difficult task until now [1]. There are a number of reasons for that. No instruments capable of noninvasively recording data on hemodynamics and metabolism, as well as the cardiovascular system performance, could be used.

Evaluation of general repolarization of cardiomyocytes with biphasic pulses of different shapes
Nikolay N. Chernov, Aleksandr A. Bezverkhii, Vladimir I. Timoshenko

According to data provided by the European Resuscitation Council (ERC), 76% of sudden cardiac arrests should be attributed to ventricular fibrillation. The main treatment of this disease is an immediate cardiopulmonary resuscitation, one of the components of which is a defibrillation of abnormal rhythms.

Polynomial filtering of low- and high-frequency noise for improving the accuracy of ECG signal processing: new advancements
Yeldos A. Altay, Artem S. Kremlev

The article describes a solution of the ECG signal processing problem in the presence of low- and high-frequency noises, which reduce the accuracy of selection of the signal informative parameters during their processing. To increase the accuracy of the signal informative parameters selection, developed is a new method for noise filtering based on a polynomial approximation of high frequency filters and wide-band reject filters using Newton polynomials.

Review of the recommender systems application in cardiology
Konstantin V. Kamyshiev, Viktor M. Kureichik, Ilya M. Borodyanskiy

The article provides a review of the recommender systems application in medical field, cardiology, in particular. The concept of recommender systems is defined, the brief history of the recommender systems development is given. The main types of recommender systems and principles of their construction are presented. The advantages and disadvantages of the recommender system methods application in cardiology are identified.

Effects produced by electrode characteristics on the accuracy of formation of electrical cardiac signal parameters
Yeldos A. Altay, Artem S. Kremlev, Sergei M. Vlasov, Alexey A. Margun, Konstantin A. Zimenko

Our results of analyzing effects made by electrode characteristics on the accuracy of the ECG signal parameters formation are presented herein. Analyzed is a correlation between the measured characteristics of the electrodes and a probability value that determines accuracy of the ECG signal parameters formation. With the help of scatter plots demonstrated is the strength of the correlation between the assessed variables.

Rose Angina Score can really estimate myocardial perfusion scan results in both diabetic and non-diabetic patients?
Nasim Namiranian, Aryan Naghedi, Narges Soltani, Reza Nafisi Moghadam, Amir Pasha Amel Shahbaz, Seid Kazem Razavi-Ratki

Cardiovascular diseases are among the most important causes of mortality and morbidity worldwide. There are different risk factors explained for cardiovascular diseases and diabetes mellitus (DM) is notable among them. There are different modalities for diagnosis and risk assessment of cardiovascular diseases such as myocardial perfusion imaging (MPI) but considering high price and low accessibility of this modality we decided to assess any possible association between MPI findings and Rose angina score (RAS) in both diabetic and non-diabetic patients.

Effects produced by automated plasmapheresis on morphofunctional data on cardiovascular system performance in ischemic heart disease patients
Yury E. Malchevsky, Alikeidar A. Ragimov

We have performed the study of the effects made by the automated plasmapheresis application on ischemic heart disease clinical manifestations, echocardiographic indices and heart rate variability in patients with exertional angina III-IV functional class. It has been found that the applied plasmapheresis method is capable to reduce the severity of the disease clinical manifestations and improve the echocardiographic characteristics of the heart, in particular, reduce the level of end-diastolic volume, and increase ejection fraction. The clinical effect is already apparent at the early stages of the treatment and remains unchanged even after 6 months thereof.
Boris Ivanovich Leonov (1935 – 2020)
Doctor of Engineering Sciences, Professor.
1978 - Winner of the USSR Council of Ministers Prize. Winner of the S.I. Vavilov Prize.
1982 - was awarded the title "Best Instrumentation inventor" and "Best Inventor of Moscow."
1984 - Honored Scientist of Russia.
Since 1993 - President of Russian Academy of Medical and Technical Sciences.
Since 1984 - Director of the All-Union Scientific Research and Testing Institute for Medical Devices under the USSR Ministry of Health (VNIIMT).
Member of the Expert Council under the President of the Russian Federation, VAK RF, RAMS.
We commemorate great Russian scientist and organizer Boris Ivanovich Leonov

All-Union Scientific Research and Testing Institute for Medical Devices was established in 1951 in Moscow. Since 1985, it was headed by General Director, Doctor of Technical Sciences, Professor Boris Leonov.

Since 1993, B.I. Leonov headed the Academy of Medical and Technical Sciences. The Academy brings together prominent scientists and experts in various fields of medical and technical sciences, education, rehabilitation and prevention systems, medical industry, as well as the outstanding state and public figures, inventors, developers and manufacturers of medical equipment.

In 1988, based on the experimental plant at the All-Russian Research Institute for Medical Engineering (VNIIIMT), Scientific and Production Association "Ekran" was established.

Scientific and Production Association "Ekran" implements the scientific and technical solutions to provide the healthcare institutions with medical devices, system of products and medical technologies standardization, system developments, testing, registration and certification of medical devices; organization of manufacturing and use of medical devices and their metrological support, efficiency and safety of use as well as the development of social, legal, administrative and operational tasks, training and retraining of engineering personnel for the national health care system.

VNIIIMT provides information and technical assistance to various clinics and hospitals of the country, actively cooperates with the Moscow Higher Technical School named after N.E. Bauman. Every year increases the number of young scientists who defend candidate and doctoral dissertations in the Regional Dissertation Council functioning in VNIIIMT.

Conducted are research and development works on combating diseases that are a particular threat to the health of the nation as a whole (tuberculosis, HIV / AIDS, hepatitis B and C, diabetes, cancer, avian and swine flu, drug addiction, alcoholism etc.).

A special place belongs to the issues of standardization, certification, metrology and testing of domestic and foreign medical equipment.

Successful field of SPA "Ekran" activity is the development of mobile medical complexes for a variety of health problems, as well as for preparation of drinking water from open reservoirs and wells.

VNIIIMT has a license to issue more than 300 medical devices for different areas of medicine.
The performance of the cardiovascular system and the immunity: new philosophy in health care

Our organism works as an integrated unit. The performance of the cardiovascular system is linked with all levels of immunity. Any changes in an external and/or internal environment of an organism, including the presence of latent infectious and toxic processes initiated by pathogens of bacterial, viral, fungal and parasitic origin, affecting the organs and the systems therein, that may result in chronic diseases, find reflection in hemodynamics. The most advanced theory of hemodynamics is covered by our journal in details, and the present issue is not an exception. But we would like to note some practical recommendations on maintaining the normal immunity in healthy subjects: the recommendations have been prepared by our authors, researchers having extensive experience in theory and practice.

1. Adaptation reactions in a human organism

Professor A.I. Shikhlyarova presents her statement as follows:

Relationships between the cardiovascular system state and the adaptation reactions (AR), including the coagulation mechanisms, have been evidenced by many research works; that has found successful applications to many techniques in practice.

First of all, each AR has its own specific profile in relation to the coagulation and anticoagulation systems.

Under stress, especially in the phase of alarm, there is an increase in the coagulation potential: the R reaction time is shortened by half, and as a result the total time of coagulation T is reduced. In other words, the activity of the coagulation system grows.

With the reaction of training the diametrically opposite events occur: hypocoagulation is observed: the C clotting time becomes longer; the anticoagulation system (R + K) is activated, but moderately, not as pronounced as under the reaction of training.

Besides, when investigating the brain activity (EEG), also some rheological parameters characterizing the magnitude of systolic supply, the microcirculatory bed vascular tone, the diastolic index, the vascular elasticity have been studied that characterizes the state of the elastic properties of large-size arteries and other parameters at various adaptation reactions. There are some descriptions of these changes outlined by my monograph “Adaptation reactions and activation therapy”, 2002, page 49.

In Journal Cardiometry, Issue 15, you can find my paper treating some aspects of practical applications of AR. It offers practical recommendations on the AR type correction using conventional biostimulants.

It follows that the nonspecific basis for the cardiovascular system state, as one of the essential integral component of the organism life maintenance, is an archetype of that adaptation reaction, which performs differentiated implementation of the homeostasis regulation mechanisms under variable functional loads.

2. Increase in nonspecific resistance and immune protection of the organism

Professor E.I. Maevsky writes the following:

Succinate-based food additives: Miodon (developed by ITEB RAS, Research Center “Mioran” Ltd.) and its analogues Signalom Active and Signalom Pro Sport, produced in Canada, in addition to their capability to intensify the performance, accelerate the recovery rate of the human organism from fatigue and asthenic conditions, demonstrate their pronounced immunotropic effect, increase the nonspecific resistance and the immune protection in a human organism.

The mechanism of the action of these agents includes four main factors:

1. The primary component of this sort of food additives is succinate at doses of 10^-4-10^-5 M which activates cell receptor SUCNR1, responsible for the mobilization of the proper functions in various tissues, and especially, the hypothalamus, the heart, the kidney, the liver and the main elements of innate immunity: dendritic cells, macrophages, T and B lymphocytes.

2. The same signal doses of succinate stabilize intracellular factor HIF1α, which induces formation of the HIF dimer initiating transcription of genes responsible for the formation of the adaptation to hypoxia,
3. Small quantities of succinate activate catalytically the Krebs cycle and the associated processes of energy exchange and plastic metabolism. As a result, power supply of cells is improved, and mitochondria produce regulatory factors of the gene expression associated with the synthesis of interferon α and β.

4. The high sensitivity of the hypothalamus to exogenous succinate improves the control of the neuro-immune-endocrine system. This primarily is applicable to the activation of innate immunity, mobilizing anti-inflammatory potential of the organism and the formation of a new balance between the activity of the sympathetic autonomic nervous system and that of the parasympathetic one.

The preventive effect of these food additives has been revealed in our experiment in flu-type-virus infected pregnant mice and their descendants. There has been another trial completed: the succinate-based food additives course during a flu epidemic has reduced morbidity in patients under the ambulatory conditions and has decreased the probability of development of acute viral respiratory diseases in top athletes in their peak performance form, when the immune protection is lowered.

The above effects are determined by the fact that the components of the said food additives partially reproduce natural interactions between metabolism and the regulatory systems. The supply of the food additives in the fractional "spike" mode promotes triggering the mobilization adaptation reaction mechanisms acquired in evolution, without exhausting reserves of the organism and supporting regenerative processes.

3. Strengthening of nonspecific immunity

Professor G.A. Garbuzov has outlined his ideas as given below:

Official medicine fights viruses mostly by enhancing the specific immunity, e.g., by vaccination. It is a good decision. But in the future a vaccine is effective only under the condition that the virus does not mutate.

What should we do? Remember that the fight against any viral disease is also possible by strengthening the nonspecific immunity. This is another good decision: the way of preventive medicine.

Of course, you should avoid contacting any pathological agent: as often as possible wash your hands, use an antiseptic, exclude touching your face, especially the eyes, the nose and the mouth. Avoid visiting crowded places.

But all the measures cannot fully protect from infections. Only the immunity, which may be specific and nonspecific, can cope with it. Therefore, we have designed and prepared some phyto-compositions to enhance the nonspecific immunity.

CURCUMIN

It is the best remedy to counter pulmonary fibrosis that is the most critical complication of coronavirus. Curcumin significantly improves the structure of fibrous tissues affected not only by viral and infectious processes, but also by radiation, chemotherapy or toxic exposure.

The anti-inflammatory action of curcumin is its most important feature. Curcumin fights inflammation at the molecular level. Curcumin blocks NF-kB protein, which penetrates into the nucleus in a cell associated with inflammatory processes at the genetic level. It is precisely the NF-kB molecule that triggers inflammatory mechanisms in most chronic diseases.

In case of a coronavirus, it is advisable to suppress, extinguish excessive inflammation. Curcumin is especially reasonable to take at the beginning of the appearance of extremely high temperatures, such as 37.5 – 38 degrees, but perhaps it is more reasonable to use it preventively, from the very beginning of the virus infection. In the latter case, Curcumin should be taken immediately after the disease, for a long-term period of time till fibrosis disappears.

GINKGOTROPIL Tablets of nootropic compositions, containing Ginkgo. The brain through its neurotransmitter dopamine directs immune cells to the site of an infection at its early stages. It is the neurotrophic immune effect of the brain.

GINKGOTROPIL also contains the following:

Filipendula has an anti-inflammatory effect similar to aspirin, which moderates an overinflated inflammatory reaction produced by the organism.

Succinic acid makes mitochondria and weakened cells perform adequately, improving their oxygen energetics, thereby making them more viable and active.
NUT BUTTER “CAESAR” and “FLAXSEED”

Butters based on processed flax seed are the best source of omega-3 fatty acid, which is a powerful anti-inflammatory agent for the prevention and elimination of fibrosis. It is much better to deliver omega-3 fatty acids into the organism in the form of such food additives. The omega-3 fatty acids retard the production of molecules associated with pathological inflammation type, namely cytokines and eicosanoids, and are responsible for the production of inflammatory prostaglandins.

Methods for elimination of a secondary infection

In case of a secondary infection we consider it is better not to use antibiotics, which are more suitable for the obligate type of pathogenic bacteria and acute phases of the disease, since they make numerous side effects, therefore we think it is better to use harmless natural remedies. Here below are the best of them.

SILVER WATER

It is a multi-purpose antiviral and antibacterial remedy. Its main feature is that it has a nonspecific action, i.e. it is not aimed at elimination of any particular pathogen, but at a wide range thereof. Viruses cannot adapt to the remedy, whereas they periodically adapt to other drugs, as is well known on the example of the flu, when every year there are new strains thereof. Being accumulated on a membrane of a sick cell, silver ions first deprive it of its ability to divide, and then penetrate into the membrane, blocking the cytoplasmic membrane and disabling the enzyme functions of the bacteria. After these actions the pathogen dies. It is known that silver water, produced with electrolysis method, kills viruses in most effective way. You can take 1-2 tablespoons of silver water every day and rinse your throat, nose and even make inhalation.

MYRTABIOTIC

It is produced on the basis of the myrtle, which has a unique strong therapeutic effect. The curative effects of the myrtle are attributed to the availability of essential oils, as well as polyphenols, flavonoids and saponins found in the myrtle leaves.

STOPRAZIT 9

It is a complex multi-purpose antiparasitic drug against all types of parasites, which may suppress the functioning of our organism and weaken its protection potential. Numerous species of parasites, which may colonize our organism, may be the cause of many chronic diseases and weak immunity. Once a year each person is recommended to complete a comprehensive program of removing them. It can greatly strengthen the organism’s defense.

JUGLONE-premium Extract of Black Walnut

It prevents the spread and multiplication of a pathogenic microorganism, which weakens the organism’s resources. Juglone is usually taken as a second course after STOPRAZIT 9. It is required because Stoprazit 9 struggles well against adult forms of parasites, but their eggs and cysts remain unaffected, so that they 1-3 months later can wake up and infect the organism again. And therefore needed is the second course with Juglone as it is the best soft remedy to kill adult forms of parasites.

Reasons for combining methods both of specific and nonspecific medicine

It is known that 80% of the patients infected with COVID-19 show little to no symptoms or demonstrate subclinical symptom patterns. This should be treated as evidence for successful activation of the nonspecific immune system response in this sort of infected individuals. Consequently, it would be of advantage if as many people as possible would experience this mild form of the virus disease: that might result in a sharp
Let us separate TWO PRACTICES from a large toolbox designed to raise both the specific (immunity) and nonspecific protection of our organism, capable in one case to prevent infecting and in another one avoid developing severe complications including atypical pneumonia.

The first PRACTICE is self-acupressure, one of the methods of reflexology, which can be used by every individual at home. Hereby we are offering an application of a self-acupressure technique involving consecutive treatment of 9 acupuncture zones (AZ) that has been developed by Prof. M.D. Alla A. Umanskaya.

The above technique can be successfully used even by not trained individuals. Everybody can control 9 AZ on the surface of his/her own body on a regular basis, for example, as a simple measure accompanying regular morning or evening personal hygiene routine.

In the context of this statement we should address AZ No.1. The first AZ is the most sensitive point located on the sternum. This point can be found starting with short rotating finger movements along the sternum, beginning with the manubrium of the sternum and reaching the xiphisternum. Upon the identification of a region with a higher sensitivity, you should massage the region for 30-40 seconds clockwise and counterclockwise, changing the direction upon every 9 rotations.

The second PRACTICE has been developed on the basis of the 24-hour Breathing Culture System Design discovered by Konstatin P.Buteyko, who has detected the immensity of the role of endogenous carbon dioxide (CO₂) in the human organism.

The essence of the second practice is to control your nasal breathing: you should BE A NOSE BREATH-ER for 24 hours a day. The requirement is to control your breathing: only nose breathing is acceptable, while mouth breathing should be avoided. Similar to any habit, it can be trained within one to three weeks: it depends on your own motivation and regular exercising. The motivation is very simple: nose breathing is a very reliable protection since the human nose is originally provided with all protective means to kill viruses. To train, you can use signal stickers to motivate you at home, in your office room or in your car. Use your own memes like this: Mouth breathing is toxic! Or: DI-ETARY BREATHING is my informed choice! It should be noted that on day 2 and day 3 you may “taste this breathing style”: a slight inhaling deficit. But you will be protected! Therefore, be patient, and upon several days, nose breathing style will be properly maintained by you: it will be even enjoyable. For this purpose, it would be advisable to avoid numerous conversations, especially emotionally laden debates and discussions, because...
in the circumstances there is always mouth breathing available due to the emotional state of a participant that involves breaking of the natural organism protection.

1985 the Ministry of Healthcare of the USSR published Healthcare Methodology Recommendations approved by A.M.Moskvichev, Chief of Head Department for Diseases Treatment and Prevention. They have been used as Manual to train population to apply the above mentioned simple self-acupressure techniques.

5. How to train breathing
Doctor Mark Litvak and Sergey Zaguskin recommend: Visiting site https://www.topmed.info/ru/programma-medbreathe you can find details of a simple, but very effective method how to master the proper breathing technique.

6. How to increase health margin in a human organism
Physician V.A.Lukyanchenko has prepared his recommendations as follows:

We can offer the following relevant recommendations to increase your health margin:
1. Activation therapy by L.Kh.Garkavi should be conducted on a regular basis: it may promote your organism achieving the desired levels of those activation reactions, which are capable of maintaining the high level of protection from any infection.
2. Regularly, preferably two times a day, do breathing exercises. The breathing exercise procedure “Breathing stairs” is advisable. This exercise technique should be conducted as given below: your should try to provide the same duration of each inhaling and exhaling, and the duration in each subsequent cycle should be incremented by 0,5 seconds, respectively (you can simply count it). It looks like this: one – inhale=one exhale; one-two – inhale= one-two exhale etc. reaching your own possible maximum count. Upon reaching the maximum result, you should do it in the reverse order, i.e. gradually decreasing the inhaling and exhaling duration. Upon every training course, you will note that your upper limit is increased: it will be an indication of strengthening of your personal health margin.
3. It is advisable to perform simple push and pull exercises like jumping, striking, object throwing etc.
4. Improvement of buffer-type systems in the organism are recommended, too. For example, for a short time, say 10 days or so, do every day the following: 1/3 tea spoon bicarbonate of soda should be slaked with 30 ml boiling water, mixed till quenching is completed. Add 200 ml water to the quenched mixture and drink it 40-60 minutes before your meal.
5. Strengthening of the glutation-peroxidase system: soft-boiled eggs, broccoli one hour before to go to bed.

The above measures to be taken on a regular basis are capable of increasing the health margin in a human organism and providing an adequate response by the immune system to a virus infection. All the above recommendations have been tested and experimentally verified: they have demonstrated their effectiveness.

7. Genome expression induced by some specific low-intensity electromagnetic field frequencies as an effective way to improve the immunity response
Developers of Device EZh-2 (“Energy of Life”) www.эж2.рф designed for noninvasive physiotherapy present their opinion as follows:

In our everyday life everybody is exposed to a great variety of natural electromagnetic fields and waves including those generated by different biological objects. Some of the EMF types can be used to maintain the normal biophysical processes in living organisms. Provided that the mass values of living cells, proteins etc. in a human organism are known, with treating them
by exposure to some specific resonance frequencies, it is possible to restore their normal functioning. The developers of the above-mentioned device have carefully studied and analyzed the resonance spectrum of human ECG frequencies, and involving the data on the Earth's natural frequency background, they have designed and manufactured a device to restore the resonance frequencies of a membrane in a living cell. In their experimental studies, the designers of the EZh-2 device have discovered that a contactless exposure of soft tissues in a human organism to some specific broadband carrier signal frequencies, correlated with the relevant types of adaptation reactions in a human organism according to the concept by A.I. Shikhlyarova, can relieve pains of different origin. Upon completion of the deeper experimental studies, it has been detected that after the above exposure the immunity effectiveness is 3 to 5 times higher as compared to the initial state. An assessment of effectiveness has been carried out on the basis of values of ratio thymus mass/adrenal glands mass. Table 1 herein below shows that the value of this ratio, treated as a marker of the immune system performance, upon completion of the EZh-2 therapy has reached an average value of 3. This is much higher than it is the case with any medication therapy. And there is one more advantage of the EZh-2 therapy: no adverse effects are available.

The effective applications of the EZh-2 device during several years have demonstrated its high general efficacy: you can find more details upon visiting site www.эж2.рф. It should be noted that the device is user-friendly: it is designed for intuitive users at home.

The processes, which are initiated by an influence made by some specific low-intensity electromagnetic fields, are associated with genome expression. In particular, upon the above specific MF exposure, hypoxia inducible factor HIF1α is initiated. As noted by E.I. Mayevsky, in this case, as a result from transcription of genetic information from hypoxia response element HRE, a considerable spike-type acceleration of synthesis of a number of adaptive proteins takes place. As a consequence, glucose supply to the cells is increasing, and glycolysis as main ATP source under oxygen deprivation is activated, erythropoiesis and angiogenesis are induced in hypoxia affected tissue regions. This promotes the stable activation of anaerobic and aerobic energy-crediting processes, provides more complete oxidation of all energy-producing substrates and removal of incompletely oxidized metabolites. So, we may conclude that the HRE mobilization makes possible to achieve the desired long-term favorable effects. In this connection, we should mention that the Nobel Prize in Physiology or Medicine 2019 was awarded jointly to Kaelin Jr, Sir Peter J. Ratcliffe and Gregg L. Semenza “for their discoveries of how cells sense and adapt to oxygen availability.” They identified molecular machinery that regulates the activity of genes in response to varying levels of oxygen.

In our opinion, applications of the low-intensity EMF resonance frequencies hold much promise. But there is a challenging task to identify individual resonance frequencies of viruses that is required to take proper measures in supporting our natural immunity and disabling any virus activity.

**Conclusions**

To finalize the statements and opinions presented herein by our experts, who have a vast practical experience, we would like to note capabilities and possibilities of cardiometric diagnostics. The cardiome-
try-based method of the cardiac cycle phase analysis is capable of identifying an imbalance between the systemic and pulmonary circulation in the most accurate way. The cardiometric technology is easy in use, accessible and delivers a lot of valuable data. The technology can be used now and here. You can find more details pertaining to cardiometry in our book free available under www.cardiocode.ru.

Prof. V.A.Zernov
Prof. M.Y.Rudenko
Editorial CARDIOMETRY
The metabolism rationale for applying of succinate-based compositions to maintain high performance in a human organism

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Abstract
Design of an effective succinate-based agent for the use in sports has required a profound analysis of the main action mechanisms of the agent in question. Our paper reflects basic principles, which are decisive for the design of the offered succinate-based agent to increase the organism performance and the rate of recovery after intensive physical loading. We have treated a special role of the metabolic conversions of succinate in energy exchange of mitochondria: high energy efficiency, possibility of beneficial oxidation under oxygen deprivation, anaerobic formation and possible consequences of the above phenomenon. The listed key factors have determined the applications of succinate in practice in order to maintain the energy exchange as well as design a number of anti-hypoxia means. It is assumed that the treated peculiarities of the succinate metabolism can provide the basis for formation of a signal, regulatory role of this molecule in the organism environment.

Keywords
Succinate, Metabolism, Succinic acid, Hypoxia

Introduction
For thousands of years there have been created legends and tales of healing properties assigned to amber powder and amber oil [1]. One of the first documented cases of pharmaceutical uses of succinic acid is Hagers Handbuch published in German and Russian since 1856 till 1999 [2, 3]. Known is the St.Peterburg’s version “Handbook of Pharmaceutical and Medical & Chemical Practice” dated back to the XIX century. It is interesting that at that time to normalize the human condition, recommended have been succinate-based composition “Mixtura tonico-nervina Stahl”.

Participation of succinic acid (SA) in the metabolic processes has been discovered much later: in 1910 by Battelli and Stern [4]. In the 1930th Gozsy B. and Szent-Gyorgyi A. as well as H.A. Krebs in his autonomous research in parallel have identified and established the SA participation role in oxidation & reduction conversion processes in the energy exchange [5, 6] in the tricarboxylic acid (TCA) cycle, which is also known as the Krebs cycle. This discovery has promoted studies and design of pharmaceutical succinate-based compositions (SBC) targeted at the maintenance of the cell energetics under loading conditions. At present, there are succinate-based agents available, which are used in treatment of brain ischemia [7] and blood loss [8]; there are also parapharmaceutical Biologically Active Additives (BAA) on the succinate basis known, which prevent development of meteopathy [9], are beneficial in mitigating menopausal syndrome [10], elevating the human performance [11, 12] and the resistance to alcohol intoxication [13, 14]; the family of these substances includes some veterinary drugs, too [15], etc. Described has been a great variety of exemplary cases of applications of different SBC types in medicine and veterinary [16, 17, 18]. The range of the above SBC products includes well-known Reamberin, Limentar, Mexidol, Yantarvit, Mithomin, Enerlit-Klima, Amberen, Potensa, Antip, RU-21, Mithocalcedar etc. The other family of the products designed for elevation of the performance offers Enerlit, YantarIn-Sport, Miodon, Signalom active and Signalom pro Sport. Initially, the idea of the SBC developers has been to use them as a succinate source to maintain the cell energetics. Therefore, we consider first of all the participation role of succinate in metabolic conversions, which are directly linked with intense physical loads.
Succinic acid as an intermediate in the energy exchange

Within the Krebs cycle, succinic acid (SA or succinate) is produced as a result from the oxidative decarboxylation of α-ketoglutarate and the progress of the succinate tyokinase reaction. The next step is when SA (succinate) is oxidized to fumarate by succinate dehydrogenase (SDH), which is not only a ferment in the TCA cycle, but also complex II in the respiratory chain of the mitochondria. The papers by Chance B. [19], Kondrashova M.N. [20, 21, 22] and some other researchers have demonstrated that there is a uniquely high power output produced by mitochondria due to succinate oxidation. The process of the succinate oxidation outperforms all intermediates found in the energy exchange for the oxygen consumption rates and the ATP synthesis, value of the transmembrane electrochemical potential of hydrogen ions $\Delta \mu \text{H}^+$, generated on the inner membrane of mitochondria, as well as for the capability to maintain energy-dependent processes like reverse electron transfer (RET) or accumulation of the $\text{Ca}^{2+}$ ions. The succinate oxidation results in a release per time unit of much greater energy equivalents than it is the case with the oxidation of any other substrate in the TCA cycle or any fat acids in the β-oxidation reactions.

M.N.Kondrashova and her Scientific School have presented their own concept of a special role of the succinate oxidation in mitochondria in energy supply required for the functioning cycle “rest – performance – recovery” [20, 21, 22]. This concept has played a leading role in the proper understanding of the fact that a high energy power due to the succinate oxidation is a prerequisite for a success in the use of SBC under high energy consumption conditions, or energy deficit and acidosis, under adaptation to heavy loads and post-loading recovery [23].

Anti-hypoxia effect produced by succinate-based compositions

The most vivid example to illustrate the succinic oxidation and formation features can be found under hypoxia. Acute hypoxia ranging up to anoxia is attributed to most functional loading cases and should be considered to be at the root of many adaptive and pathological states. It should be remembered that even under normoxia there can be detected some hypoxia-affected areas, which may appear due to heterogeneity in oxygen supply of different areas in tissues, cells and mitochondria [24, 25]. Tissue heterogeneity in the pO2 distribution can be explained by different lengths of the diffusion path used to transport oxygen to the cells located at different distances from the respective blood vessels. And in addition, it is well known that at rest not all of the capillaries are involved in the operation. Therefore, the farthest cells, which are located at the greatest distances from the arterioles and the artery part of the capillary net, are affected by hypoxia. The same is applicable to the mitochondria located at the greatest distances from the cell surface. Under a considerable surge in the tissue functional activity, there is mismanagement or discord between a relatively slow and/or deficient mobilization of the blood circulation system plus oxygen transport, on the one hand, and a very fast transition of the cells and tissues from their rest to their activity, on the other hand. The most pronounced disagreements in the energy demands can be established between the cells being at rest and those being active in the excitable tissues, which are found in our heart, skeletal muscles and of course our nervous system. Energy expenditures required by the excitable tissues may rapidly grow by a factor of ten and over. As a consequence, the amount of the tissue pO2 decreases, the number of hypoxia-affected areas rises and some temporarily available zones of anoxia appear. In our further considerations, we dwell on differences in conversions of SA in the TCA cycle under the hypoxia and anoxia or anaerobiosis conditions.

Due to high affinity of citochrome oxidase for oxygen, the transport of the reductive equivalents and the oxidative phosphorylation in the respiratory chain is maintained even under deep hypoxia. Lowering oxygen concentrations up to 04,–0,7 µM does not stop functioning of complexes II, III and IV [26, 27]. But it has been revealed that the redox state of respiratory carriers and cytochrome oxidase in tissues are more sensitive to a decrease in pO2 [27, 28] as it is the case in vitro. In particular, for the first 5 seconds under heavy hypoxia (with an oxygen concentration at a level of 20 µM), in isolated tissue sections, pyridine nucleotides are much greater reduced than the other transporters in the respiratory chain [28]. The same differences have been reported for a perfused organ during the transition from normoxia to anoxia [29]: in the hypoxic transition state, practically full reduction of pyridine nucleotides has been observed with a sufficiently high degree of the oxidization of flavoprotein.
As a rule, under the hypoxic conditions, the oxidation of the NAD-dependent substrates is disrupted, the NADH/NAD ratio significantly grows, and some preconditions for the prioritized oxidation of succinate are generated [30]. It has been detected that complex I is highly sensitive to actions of a great variety of damaging factors and inhibitors, represented by different lipophylic compounds [31, 32]. Besides, it has been established that complex I can lose its prosthetic flavine mononucleotide group [33, 34]. Due to an effect of increased concentrations of the nitrogen monoxide and other nitrolyzing compounds, formed in the cell under oxygen deficiency conditions, complex I leaves its active state A for its inhibited state D [35]. Barbiturates, acetaldehyde and rotenone reproduce this situation and make it possible to simulate it in vitro with the total inhibition of complex I and consumption of oxygen in the oxidation of NAD-dependent substrates, for example, β-oxybutirate (see Figure 1 herein). It has turned out that of great importance are the presence of electronophylic metabolites like oxaloacetate and the progress of the fumarate reductase reaction that promotes the succinate formation by the reductive conversion in the Krebs cycle. Owing to functioning of complexes II, III, and IV [26, 27, 36], succinate produced due to a high level of NADH is immediately oxidized (see Figure 1A herein). Malonate as the SDH inhibitor stops both the succinate oxidation and the fumarate reductase reaction. According to recorded data on the malonate-sensitive oxygen consumption in the presence of rotenone and by generation of transmembrane potential ΔΨ (see Figure 1B herein), we can estimate dynamically the contribution of the NAD-dependent substrates, for instance of α-ketoglutarate or some mixtures of substrates like α-ketoglutarate with aspartate, or malate with pyruvate etc., to the succinate formation.

The prioritized oxidation of succinate under hypoxia (against the background of a high degree of the NADH reduction) is provided by the availability of the oxidized flavoproteides and coenzyme Q and a flow of the reductive equivalents at the terminal portion of the respiratory chain. It is interesting that even under normoxia (really under hyperoxia in the incubation cuvette) in state 4 according to B. Chance and G.R. Williams [36], due to an increase in the degree of the NADH reduction, observed is the prevailed oxidation of succinate that is recorded by loss of radioactivity of a radioactive tracer in vitro in the intact rabbit’s heart.

Figure 1. Addition of rotenone into suspension of respirating mitochondria suppresses oxygen consumption (A) in the oxidation of β-oxybutirate (β-OB). By adding α-ketoglutarate (α-KG) we can easily restore the respiration of mitochondria with aspartate (ASP), malate with pyruvate or α-ketoglutarate with ammonia. The proper full-scale transmembrane potential is generated under the oxidation of the added succinate. The incubating medium has been composed as follows: 250 mM sucrose, 10 mM tris-HCl (pH 7.4), 10 mM KCl, 3 mM MgCl2, and 3 mM KH2PO4. Concentration of mitochondria is 3 mg per ml; t 26°C. All substrates have been added with a final concentration of 5 mM. DNP – 30 µmol, rotenone -10 µmol. Oxygen consumption data have been recorded with polarography. The transmembrane potential has been measured with the use of the selective electrode according to changes in concentrations of the lipophyl cation of tetrathioniphosphonium (TPP+).
In state 4, a high value of the ATP/ADP ratio for the mechanism of the respiratory control retards the flow of the reductive equivalents that results in an increase of the NADH/NAD+ ratio. During the oxidation of the traced pyruvate in mitochondria, a non-proportional drop of the tracer concentration in succinate (contrary to the theoretical stoichiometry of TCA) in state 4 is detected. Conversely, in state 3, when values of both ratios NADH/NAD+ and ATP/ADP sharply decrease, a non-proportional accumulation of the tracer in succinate appears, while it lowers in the intensively oxidizing NAD-dependent substrates [37].

The priority of succinate to be oxidized in vivo under the hypoxia conditions can be evidenced by almost doubled drop of the succinate concentration in the liver in rats placed in an altitude chamber, when simulating the true altitude conditions of 8000 m [23]. It has been demonstrated by N.A.Glotov that upon staying “at the above elevation” for 2 hours, a significant reduction in the succinate concentrations in blood, the liver, the heart and the kidney in the rats has been reported, while a doubled concentration of the NAD-dependent substrates has been detected [38]. An indirect argument in favor of the prioritized oxidation of succinate under an arbitrary, short-time, for 40 seconds, breath holding, is an abnormal decrease in the value of the respiratory coefficient \( R = \Delta C_{O_2}/\Delta O_2 \) up to 0,45÷0,55 in the first portion of the exhaled air [39]. Under eupnea, the R value in volunteer test subjects has been reported to reach 0,95÷0,97. We think the observed decrease in the R value reflects the oxidation of those substrates, which have not been subjected to decarboxylation (in the absence of anywhere pronounced respiratory acidosis). In this connection, first and foremost succinate can be classed with the above type of the substrates. The oxidation of lipids is accompanied by a decrease in the R value to 0,7. It should be noted that with developing respiratory acidosis the R value can exceed 1,0 due to an increase of pCO₂.

Some researchers believe that it is precisely the possibility to retain the oxidation of succinate that favors the maintenance of the oxidative phosphorylation under hypoxia [8, 23, 28, 30, 36, 37,]. So, we can summarize it as indicated in Figure 3 herein: inhibition of the oxidation of the NAD-dependent substrates at the level of complex I and the prioritized oxidation of succinate under hypoxia.

### Anaerobic formation of succinate in mitochondria

Under the anaerobic conditions, in the suspension of isolated mitochondria, similar to an organ with an interrupted blood supply, just upon expiration of several seconds, a ten- to fifty-fold accumulation of succinate can be easily found [40-47]. Hochachka P.W. and G.N. Somero have described a spike of endogenous succinate concentration at the level of the organism as a whole in deep-sea animals and divers [48]. Usually the TCA cycle reductive conversion of oxaloacetate is assumed to be a source of succinate.

\[
\text{Glucose} \rightarrow \text{Pyruvic acid} \rightarrow \text{Malic acid} \rightarrow \text{Succinic acid} \rightarrow \text{Fumaric acid} \rightarrow \text{Oxaloacetate} \rightarrow \text{Gluconic acid} \rightarrow \beta-	ext{Ketoglutaric acid} \rightarrow \text{Glutamic acid} \rightarrow \text{Ascorbic acid} \rightarrow \text{ROS} \rightarrow \text{O}_2 \rightarrow \text{ATP} \rightarrow \Delta \mu \text{H}^+ \rightarrow \Delta \mu \text{H}^+ \rightarrow \text{ADP} \rightarrow \text{ATP}.
\]

Figure 2. Against the background of the hypoxic inhibition of the oxidation of the NAD-dependent substrates [26, 27, 35], the oxidation of succinate is further maintained. SDH delivers a pair of electrons into the respiratory chain irrespective of the degree of the NADH reduction and functioning of complex I. It has been shown that the energy released during the transfer of the pair of electrons (2e) through the respiratory chain to oxygen is converted into transmembrane electrochemical potential \( \Delta \mu \text{H}^+ \). With the use of complex V – ATP-synthase, \( \Delta \mu \text{H}^+ \) provides for phosphorylation of ADP to ATP. Despite a decrease in the ATP/O value, a high rate of the succinate oxidation under the maintenance of functioning of complexes II, III, IV and V makes possible to keep a sufficiently high energy efficiency of the oxidative phosphorylation. It has been also shown a single electron leakage promoting generation of oxygen superoxide \( \text{O}_2^- \) as a progenitor of other reactive oxygen species (ROS).
We have measured with the use of H1 Nuclear Magnetic Resonance (NMR) spectroscopy in accordance with the NMR technique by O.I.Pissarenko [40] theoretically possible pathways of accumulation of succinate under the stopped respiratory chain in the mitochondria in the heart, the renal cortex and the brain in rats and guinea pigs [23]. As it is evident from data given in Figure 3 herein, we can identify in the examined mitochondria at least three metabolic pathways of the anaerobic formation of succinate (AFS).

The most known AFS pathway is the reductive conversion in the TCA cycle from oxaloacetate (OAA) or malate (see Figure 4 A). The most powerful AFS pathway is represented by coupled fluxes, when the reductive conversion in the TCA cycle supports the oxidative part of the TCA cycle (see Figure 4 B herein).

And, finally, the anaerobic dismutation of α-ketoglutarate according to Krebs-Kohen [49] in the presence of excess of ammonia (of the order of 1-1,5 mM) takes place (see Figure 4 C). In this case, under intense loading, deamination of adenylate nucleotides due to energy deficit is the prime contributor.

We have demonstrated in the schemes given in Figure 5 the anaerobic pathways of succinate formation in that step sequence (A, B, C), which is implemented in mitochondria without regard to from what tissue they have been separated. Initially, against the background of the preserved oxidative phosphorylation, process A has taken place. A driving force for this is a high degree of the reduction of NADH and the oxidative phosphorylation due to an increased level in ADP and non-organic phosphate. The next step is oxidation: process B is started due to the appearance of NAD+. As endogenous ammonia is de-energized and accumulated, process C is initiated: it’s the anaerobic dismutation of α-ketoglutarate. By the example of mitochondria in the heart as indicated in Table 1 herein, a typical contribution of these pathways as a percentage of the AFS value in consecutive time intervals under the anaerobic incubation of mitochondria.

### Table 1

<table>
<thead>
<tr>
<th>Pathway of anaerobic formation of succinate</th>
<th>Duration of anaerobiosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Reductive conversion in TCA</td>
<td>3 min. 4.5 min. 6 min. 7.5 min.</td>
</tr>
<tr>
<td>B. Coupled oxidation of α-ketoglutarate</td>
<td>– 51% – –</td>
</tr>
<tr>
<td>C. Anaerobic dismutation of α-ketoglutarate</td>
<td>– 11% 100% 100%</td>
</tr>
</tbody>
</table>

Figure 3. The H1-NMR spectra under mitochondria incubation (16 mg of protein per ml) in the rat liver with different substrates under the closed respiratory chain at the level of complex III with antimycin A (0,35 μg/mg mitochondrial protein). Cuvette volume is 0.5 ml, t 26°C. Incubating medium composition: 100 mM KCl, 3 mM KH2PO4, 3mM MgCl2, 0,5mM EGTA, 0,4 mM ADP, 2 0 mM tris-HCl buffer (pH 7.4) and 2,5% D2O. Substrates(A – 5 mM malate, B – 5 mM aspartate and 5 mM α-ketoglutarate, C – 5 mM α-ketoglutarate and 2,5 mM NH4Cl. Each curve is a result of 90 accumulations for 90 seconds. There are curves upon 3 and 9 minutes of mitochondria incubation.

(Operated by M.S.Okon with NMR-Spectrometer [50]).
Figure 4. Scheme of anaerobic formation of succinate in mitochondria in different organs. The reductive conversion in the TCA cycle due to excess of NADH from oxaloacetate (OAA) to succinate (Figure 4 A) takes place under participation of malate dehydrogenase (1), fumarase (2) and SDH undertaking the role of fumarate reductase (3). In the fumarate reductase reaction oxidized are the reduced flavoproteid and Coenzyme-Q. This is responsible for the fact that the reductive equivalents are transferred from complex I to the oxidized Coenzyme-Q, and the oxidative phosphorylation of ATP (4) [51-55] occurs. The OAA source may be aspartate (ASP) in the aspartate aminotransferase reaction (5), phosphoenolpyruvate (PEP) in the phosphoenolpyruvate carboxinase reaction (6) and pyruvate (PYR) in the pyruvate carboxilase reaction (7). Reaction (6) in rats is presented to 95% in the cytosol, while that in pigeons, guinea pigs, rabbits and human individuals appears practically equally in the mitochondria and cytosol. Under the stress conditions, activity of the cytosol phosphoenolpyruvate carboxinase significantly rises: hormonal induction of synthesis de novo takes place. Figure 4 B (coupling of two AFS flows): the reductive conversion in the TCA cycle from OAA to succinate (1) favors the oxidation of NADH to NAD+, which is reduced in the usual progress of the oxidative reactions in the TCA cycle, among them in the progress of the oxidation of isocitrate and α-ketoglutarate to succinate (2). In this case, the oxidative phosphorylation occurs in the same manner as it is the case with situation A in the course of the reductive conversion in the TCA cycle. At the same time, the substrate phosphorylation of GTP at the level of succinyl-CoA, formed as a result from the oxidative decarboxylation of α-ketoglutarate, takes place. Under the anaerobic dismutation of α-ketoglutarate (see Figure 4 C) [49], in the glutamate dehydrogenase reaction (1) NAD(P)H is oxidized due to the reductive amination of one molecule of α-ketoglutarate to glutamate. The oxidized NAD(P)+ is reduced by transhydrogenase at the expense of NADH (2). For this purpose, is required generation of ΔμH+ of the order of 100 mV that is twice less than required for the ATP phosphorylation. The NAD+ oxidized by transhydrogenase and reductive amination favors the oxidative decarboxylation of another, the second, molecule of α-ketoglutarate (3) to succinyl-CoA, which provides for the substrate phosphorylation (4) of GTP. Nucleoside diphosphate kinase (5) discharges a small pool of GTP by transfer of phosphate to ADP: ATP is formed. It is conceivable that it is just ATP that is used to maintain ΔμH+ required for the transhydrogenase reaction (2).

So, under the anaerobic conditions in the TCA cycle, succinate is formed and accumulated similar to the case when lactate is stored in the anaerobic glycolysis.

It is of importance that, as opposed to anoxia, under hypoxia, when we deal with heterogeneity in the pO₂ distribution, both AFS and the succinate oxidation may take place at the same time, in parallel, in different areas. Where the anaerobic conditions are available, SDH operates as fumarate reductase, with reducing fumarate to succinate. In those areas, where higher pO₂ values are found, the terminal portion of the respiratory chain is in operation, and SDH functions as succinate: coenzyme-Q-oxidoreductase. In doing so, a fumarate-succinate shuttle is provided. First the fumarate-succinate shuttle has been detected between the lungs and peripheral tissues under hypoxic exposure in animals [54]. We suppose this sort of shuttles takes place between the mitochondria in cells and between the cells within the same tissue type due to heterogeneity in the pO₂ level in different areas and in the degree of the reduction of the respiration-related carriers.
Consequences of anaerobic formation of succinate (AFS)

Originally AFS in mitochondria have been considered as an exclusively adaptive process, which favors formation of energy-rich compounds and maintenance of the functional condition of poly-ferment systems in mitochondria in the absence of oxygen. It has been suggested that an additional bonus in this case is a fast way to tackle an energy deficit under the re-oxygenation due to the oxidation of the accumulated succinate. Of course, the energy-yielding role of AFS in mitochondria is small and cannot meet even the basic requirements of mitochondria in the TCA cycle with the stopped respiratory chain (see Figure 5 A herein). The energy output from AFS may only cover the requirement to avoid a sudden drop in the ATP/ADP ratio for 3-6 minutes under the blockade of adenylate translocase by carboxy-atractyloside and ATPase in mitochondria by oligomycine (see Figure 5 B herein) [50].

It is probable that AFS in cells under the anaerobic conditions is a minor energy source, which is available in addition to glycolysis [23]. So, under the cold cardioplegia conditions, with suppression of the energy consumers in the intentionally arrested heart, when the blood supply is interrupted, the beneficial contribution of AFS to the intactness of the myocardium is most pronounced [44-46].

Reperfusion damage and oxidation of the accumulated succinate

A large body of research papers shows that a post-ischemic oxidation spike of succinate accumulated in the heart is combined with an explosive acceleration in formation of reactive oxygen species (ROS), which are responsible for development of post-ischemic reperfusion damages [56-62]. An intensive formation of ROS at the moment of reperfusion is determined by a rapid pO2 growth. It is favorable to free-radicals’ single-electron leakages with the reduced carriers – the formation of ROS, which increases in proportion to the pO2 value in a wide range of the oxygen concentrations, even in the transition from normoxia to hyperoxia. It has been demonstrated that the process of generation of ROS in mitochondria can be provided in full only in the case, when the ΔμH+ value exceeds 150 mV [58-60]. However, it has turned

Figure 5. Changes in the energy condition of mitochondria in the rat’s liver under AFS. Legend: A: The [ATP] and [Pi] dynamics in the presence of α-ketoglutarate and aspartate with the traced change in the AFS pathways. ATP and phosphate concentrations are estimated according to the respective 31P-NMR spectra. B: The [ATP] dynamics in the mitochondria suspension under incubation in the presence of different substrate sources of AFS and two inhibitors at the same time: 10-5M carboxy-atractyloside (inhibitor of adenylate translocase) and 10-5M oligomycin (inhibitor of H+ATPase). The incubation conditions are the same as shown in Figure 3 above herein.
out that the pO2 level and the ΔμH+ value or the electrical ΔΨ thereof and the ΔpH component are not the leading factors in the ROS generation. The key role plays a high degree of the reduction of the respiration carriers in complexes I and III, which are maintained in the presence of oxygen due to a high ATP/ADP ratio in state 4 according to Chance B.- Williams G.R. 

Hence it follows that in case of the oxidation of succinate, which is accumulated in excess after ischemia, the situation with generation of ROS is not so simple as it is reported in many papers including those mentioned by us [57,58]. There is a lot of research works, which demonstrate a direct relationship between the excess generation of ROS and the oxidation of the succinate excess and active operation of ADH (succinate dehydrogenase, succinate: ubichinon oxidoreductase) with the reduction during the reverse transfer of electrons (RTE) of complex I as well as a rapid growth of the degree of the reduction of components in complexes II and III. However there is little likelihood thereof [62], for at least one reason: at the moment of reperfusion, plenty of ATP consumers reproduce active state 3, i.e. an excess of ADP and even uncoupling of the oxidative phosphorylation. In the circumstances, neither maintenance of a high ratio NAD(P)H/NA-D(P)+ or keeping of a great value of ΔμH+ is possible, since de-energization and destroy of intactness of the membranes in mitochondria take place.

In the above mentioned experiments on AFS we have estimated the phosphoryl potential (the ATP/ADP ratio and the pool of adenyl nucleotides) and the maintenance of respiration control (in our experiment it has been shown as dependence of the AFS rate on the ATP/ADP value in isolated mitochondria). It has been evidenced that even in vitro under relatively comfortable conditions (the closed system), namely free of calcium overloading, without external ATP consumers, in the presence of excessive substrates, at a temperature decreased to 26°С, de-energization of mitochondria and uncoupling of the oxidative phosphorylation inevitably take place that is growing for 9 minutes of the incubation with the stopped respiratory chain [23]. This situation has been treated in detail in experimental works and reviews [60, 61, 62, 63]. In the cells, a heat-associated ischemia, reperusions against the background of not isolated energy consumers, post-ischemic calcium overloading and opening of the mitochondrial permeability transition pore (PTP) hinder maintaining ΔμH+, a high NADH/NAD+ ratio and RTE. In addition, there is a pool of papers, which have demonstrated that there is protection of mitochondria from peroxidation of lipids (POL) of the membranes at the expense of the succinate oxidation [64]. Conversely, inhibition of SDH provokes enhancing of the pro-oxidant activity of mitochondria [65] and increases formation of superoxide radicals followed by developing apoptosis [66]. In vitro exogenous succinate hinders inactivation of SDH in case of initiation of lipid peroxidation by entry of Fe2+ [67, 68, 69] and inhibits the lipid peroxidation induced by the Fe2+-ad-enylate complex or potentiated by ageing of mitochondria [70]. It should be noticed that the oxidation of succinate is more resistant to damaging actions by pro-oxidants than the oxidation of the NAD-dependent substrates, in particular of α-ketoglutarate (KG) and pyruvate [54]. It follows that in order to identify in vivo specific conditions, under which oxidation of the succinate excess may produce pro- or anti-oxidant effects, required are further special investigations.

Our materials presented herein treat some metabolism-related grounds for the application of succinate and succinate-based compositions in order to maintain the energy exchange, especially under hypoxia, as well as an anti-oxidant means. However our analysis of the role and effects produced by succinate cannot cover all the aspects. The offered metabolic interpretation is based on studies on actions and effects made by sufficiently high concentrations of succinate in vitro and high dosages of succinate in vivo, which are comparable to those millimolar concentrations, which are capable of producing a direct effect through their participation in the metabolic processes. There are not so many physiology grounds for the interpretation of the above matters, at least due to the fact that succinate delivered via the the stomach and the gastro-intestinal system is intensively used by the epithelium of the stomach and the bowel, the microbiome, the liver etc. As a result, only very small quantities of exogenous succinate can reach mitochondria in other tissues in the organism. Studies conducted for last decades have considerably extended the conceptual scopes of possible succinate application effects on the human organism. In this connection, we should mention that discovered and widely studied is the role of exomitochondrial succinate as stabilizer of the cytosol transcriptional adaptational hypoxia-inducing factor HIF1α [71]. It has been established that extracellular succinate is a specific ligand of the cell succinate
receptor SUCNR1 [72], which is called by some researchers a stress-receptor. The special role played by succinate in metabolism of mitochondria has been justified and preserved by evolution at the regulatory level in the systems of higher hierarchical levels. This scientific field requires further particular treatment and a thorough analysis.

Statement on ethical issues
Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest
None declared.

Author contributions
The authors read the ICMJE criteria for authorship and approved the final manuscript.

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Cardio-oculometric indicators of psychophysiological readiness of students to examinations

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Abstract
Cardio-oculometric indicators to grade psychophysiological readiness of students to examinations are described herein. Given is an experimental evidence that transitions from a low level of psychophysiological readiness of students to examinations to a high level of such readiness thereto is really accompanied by significant changes in the organism performance, first of all, in that of the heart. It is shown that a reliable marker of such changes is the heart rate variability assessment using the Baevsky stress index (SI), as well as the oculometric peculiarities of response to the visual stimuli, which students associate with their upcoming examinations.

Keywords
Cardiometry, Heart rate variability, Baevsky stress index, Psychophysiological readiness, Examinations, Unified state examination (USE), Eyetracking, Stress tolerance, Autonomic coefficient, Total deviation from the Lüscher-Valneffer autogenic norm

Imprint

Introduction
Academic examinations are one of the repetitive stress stages in life of a modern individual. As a rule, when preparing to examinations, the highest attention is focused on the cognitive component of an individual’s readiness, which relates to either a demonstration of a specific knowledge or skills of applying the knowledge in practice. But at the same time, a psychophysiological state of an individual, which is the most important component of his/her readiness to the examinations of any type, often falls beyond the scope of the focused training and is out of sight for researchers of such trainings. In this respect, even the unified state examination (USE), which is an object for stormy public and political debates, is not an exception. It seems to be at least strange against the background of tens of thousands of investigations in the field of pedagogy and sociology, which try to prove the effectiveness of the above form of knowledge assessment, considering its importance for education system and students’ training. Besides, in the early years of the USE introduction, sometimes appeared some works of psychologists with their recommendations on how students should improve the effectiveness of their preparation for examinations, but now such recommendations have been replaced by polemical notes of supporters of either negative or positive attitude towards these examinations.

It is also surprising that the issues of influence of the personological characteristics of the student as a subject in the educational activity on his/her effectiveness of coping with stress of such kind remain still insufficiently studied. But without studying the above issues, all programs of psychophysiological training to examinations become impersonal. In this case, the programs tend to formulate a set of some general-purpose guidelines, which are based, at best, on just a common sense and life experience. Their justification and possible adjustment still require a more in-depth study of relation of psychophysiological readiness and personal characteristics of the students with their success in overcoming examinations.

To a large extent, the reason for this lack of attention to the psychophysiological component of the students’ readiness to examinations is the absence of reliable means to measure this decisive component. However, taking into account our studies described earlier [1-
[12], we may assume that PC-assisted cardiographs of the Cardiocode type and modern portable eyetrackers can serve as the above mentioned measuring instrumentation. Our hypothesis takes into consideration the fact that, as shown in [1-4, 6, 8, 12], Cardiocode makes it possible to identify the nature of the respondents’ affective response to certain stimuli using heart rate variability and Baevsky stress index (SI). Eyetrackers can also be successfully employed in evaluating the personal characteristics of respondents [13]. In addition, we demonstrate in [2, 11, 12] that the level and the nature of the respondent’s stress reactions to visual stimuli can also be estimated based on oculographic data using the autonomic coefficient by Shiposh (AC) and the total deviation from the autogenic norm (TD) calculated on the basis of the Lüscher color test [15].

Materials and methods

To test the above hypothesis in the first part of our study, a complete set of subtest visual stimuli prepared as on paper sheets of the A-4 format, contained images as listed below, has been given to respondents:

- toothy jaws of an attacking vampire bat;
- a pretty image of a giant panda;
- a huge spider devouring a wasp;
- a rattlesnake preparing to attack;
- a funny kitten playing around;
- 150-point typed word EXAMINATION;
- 190-point typed word SESSION;
- a standard form of answers, which is used during the USE procedure.

During an alternate demonstration of each stimulus to respondent for 15 seconds an ECG has been recorded with the CARDIOCODE device, which allows an automatic calculation of Baevsky stress index (SI) values.

In the second part of the experiment, the above visual stimuli have been presented individually to each respondent on the screen of the GP-3 portable eyetracker. The complete set of the stimuli included the following images in this case:

- 110-point typed words GOOD MOOD surrounded by eight color squares from the Lüscher test;
- 150-point typed words EXAMINATIONS surrounded by eight color squares from the Lüscher test;
- 190-point typed word SESSION surrounded by eight color squares from the Lüscher test;
- located in the same places, eight color squares from the Lüscher test without any other images or wording;

Figure 1. Examples of the used in the parallel recording cardio-oculometric indicators upon presentation of visual stimuli

- a standard form of answers, which is used during the USE procedure.
- samples of math examination tasks;
- three runners at different distances from the finishing tape with the placed in the upper part of the stimulus wording WHERE ARE YOU?
- located in the center of the stimulus, 110-point typed wording I AM A MAN with 90-point typed adjectives SUCCESSFUL, UNSUCCESSFUL, STRONG, WEAK in the corners;
- red line with wording NOT TO CROSS THE LINE placed above the line.
- located in the center of the stimulus, 110-point typed wording YOU NEED WORK with 90-point words WITHOUT MISTAKES, RAPIDLY, EFFICIENTLY, THOROUGHLY in the corners;
- Examples of the mentioned stimuli are presented in Figure 1 herein.

When showing the above stimuli on the eyetracker screen (eyetracker) of the GP-3 type, the cardiograms of the examinees have been recorded using the Cardiocode computer-aided hemodynamic analyzer. Afterwards, using the algorithms embedded in the analyzers software, the Baevsky stress index (SI) values
have been calculated for each examinee. Illustrations of this stage are shown in Figure 2 further herein.

The following psychological tests have been used as questionnaires in the study:
- Self-efficacy score by R. Schwarzer and M. Jerusalem (translated and adapted by V.G. Romek);
- the Keirsey Temperament Sorter (KTS);
- identification of subjective conditioning or readiness to stress tests;
- the TIPI-RU questionnaire
- self-estimate of susceptibility to stressful factors (M. Friedman, R. Rosenman);
- an analysis of lifestyle (the Boston Stress Test);

In total, the study has covered 258 participants.

The statistical analysis of the obtained data has been performed using statistical package STADIA 8.0.

Results and discussion

The average SI values for various visual stimuli are presented in Table 1.

The first column of the present and all the following tables shows the numbers to indicate the visual stimuli as follows:
1 - toothy jaws of an attacking vampire bat;
2 - a pretty image of a giant panda;
3 - a huge spider devouring a wasp;
4 - a rattlesnake preparing to attack;
5 - a funny kitten playing around;
6 - 150-point typed word EXAMINATION;
7 - 190-point typed word SESSION;
8 - a standard form of answers, which is used during the USE procedure.

The static significance of differences in mean values was confirmed using the χ criterion (chi-square) that, as noted above, was evaluated using statistical package STADIA 8.0.

The obtained distributions differ from the Gauss-Laplace distribution. Therefore, in order to identify correlation relationships, we applied the Spearman and Kendall coefficients. Since the nature of the identified relationships for each of these coefficients and the factor structure revealed for each of them are similar, in the further analysis the data for the Spearman coefficient only are given because of its greater generality.

Table 2 shows the parameters of the factor structure after using the orthogonal rotation method (Varimax Rotation), with which we sought to minimize the number of variables with high loads on each factor.

In addition to the orthogonal rotation method (Varimax Rotation), we have also employed the methods as listed below:
- the quartimax rotation, with which we tried to minimize the number of factors, which are required for a meaningful interpretation of each of the variables involved;
- the equimax rotation (Equimax Rotation), which was used to simultaneously minimize the number of variables with large factor loads and the number of factors to interpret them;
- the oblique rotation (Oblique Rotation), with which we sought to minimize the number of factors without ensuring their full independence (orthogonality).
Figure 2. Demonstration of the parallel recording mode of respondent’s cardiooculometric indicators of response to the USE form presentation.

It has been found that the factor structure of the correlation relationships upon the oblique rotation (Oblique Rotation) exactly corresponds to the structure obtained after the varimax rotation (Varimax Rotation). When optimizing the factor structure of the revealed correlation relationships, we analyzed variants, which included from 3 (covered up to 80% of the dispersion and associated with larger losses of information) to 7 factors (covered over 90% of the dispersion and characterized by the presence of a significant

<table>
<thead>
<tr>
<th>Test scores</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>The USE results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress tolerance (Boston test)</td>
<td>0.418</td>
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<td>0.704</td>
<td></td>
</tr>
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<td>Subjective conditioning/readiness to USE</td>
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<td></td>
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<td>Friendliness (TIPI-RU questionnaire)</td>
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<td></td>
<td></td>
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<tr>
<td>Fairness (TIPI-RU questionnaire)</td>
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<tr>
<td>Openness to experience (intelligence) (TIPI-RU questionnaire)</td>
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</tr>
<tr>
<td>Self-efficacy</td>
<td></td>
<td>0.307</td>
<td>0.706</td>
</tr>
<tr>
<td>E score Extraversion (Keirsey questionnaire)</td>
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<tr>
<td>I score Introversion (Keirsey questionnaire)</td>
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<td>S score Sensation (Keirsey questionnaire)</td>
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<td>0.694</td>
<td>0.414</td>
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<tr>
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<td>0.328</td>
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<td>J score Judging (Keirsey questionnaire)</td>
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<td>0.307</td>
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<tr>
<td>P score Perceiving (Keirsey questionnaire)</td>
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<td>0.401</td>
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</table>

Table 5

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<thead>
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<th>3</th>
<th>4</th>
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</thead>
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<tr>
<td>Si 1</td>
<td>0.462</td>
<td></td>
<td>-0.883</td>
<td></td>
</tr>
<tr>
<td>Si 2</td>
<td></td>
<td>0.338</td>
<td>-0.618</td>
<td></td>
</tr>
<tr>
<td>Si 3</td>
<td></td>
<td></td>
<td>0.782</td>
<td></td>
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<tr>
<td>Si 4</td>
<td></td>
<td>0.894</td>
<td></td>
<td>-0.285</td>
</tr>
<tr>
<td>USE mark</td>
<td></td>
<td></td>
<td></td>
<td>0.887</td>
</tr>
</tbody>
</table>
number of less informative relationships). With Kaiser normalization, optimal has been found the optimization of the factor structure in the revealed correlation relationships, which included 3 factors and covered over 81% of the dispersion. The data for the above optimization variant is given in Tables 2 and 3 herein.

As we can see from the data presented, the SI values obtained in response to the positive visual stimuli serve as a part of the number of a sort of some factors, and the SI values upon presentation of the negative visual stimuli such as word EXAMINATION, SESSION or a USE form are part of other factors. Moreover, this regularity and the above factor structure, as a whole, are preserved for all the rotation variants used. This, as well as the fact of statistically significant differences in average SI values, also demonstrates a substantial commonality of the positive stimuli, which significantly differs from that of the substantial nature identified for the SI values for the negative stimuli.

Statistically significant Spearman correlations are detected between the USE indicators and the values in accordance with such scores as stress tolerance (0.367), susceptibility to stress (-0.343), ability to come to an agreement (0.498) and fairness (0.519) according to the Big Five Personality Test (the TIPI-RU questionnaire), score I (0.356), S (0.347), T (0.478), P (0.342) from the Keirsey Temperament Sorter. The results of the factor analysis of the complete correlation matrix with the following varimax rotation are shown in Table 1 herein.

As shown in Table 4, high results from the USE examination make a statistically significant contribution to the factor formed by high indicators of stress tolerance in respondents, their fairness and emotional stability. They are statistically significantly higher in the respondents having signs of temperaments of the ISTJ and ISTP type. As known, the success of these types of representatives in various activities is based on their intensive exercise training, participation in multiple repeatable tests of their ability to solve certain kinds of problems.

In addition to the mentioned psycho-diagnostic questionnaires for 48 examinees, who had favorable experience in successful completion of the USE, their response to stimuli used in the course of examinations in mathematics has been assessed. Sample assignments and forms to record the responses served as visual stimuli. Portable eyetracker (eyetracker) GP-3 has been employed to record the eye movement responses to the visual stimuli, the various capabilities of which in oculometric diagnostics and its beneficial application in combination with the Cardiocode PC-assisted hemodynamic analyzer are described in [5-7, 11, 12]. The time of each stimulus exposure and recording of the related cardiological data is 10 seconds. When working with each examinee, we have identified the stress index (SI) value in the organism’s regulatory systems, as conditioned by each separate stimulus, and the heart rate (HR). When working with the stimuli, the time of the examinee's sight fixation at certain fragments of the visual stimulus has been recorded with the eyetracker, and its percentage (%) referred to the total stimulus exposure time has been computed.

Arithmetic average values of the SI parameters obtained by alternate demonstration of the Lüscher eight-color table, the assignments for mathematics from the USE demo version, the USE form and phrase “good mood” on the eyetracker screen were reported to be 513, 822, 611 and 537 units, respectively. Statistical significance of the differences between these values was confirmed by calculating a chi-square parameter, the values of which in all cases were not below 1894. The correlation relationships for the listed parameters were calculated according to Spearman, the factor structure of which is presented in Table 2 herein.

Table 5 shows the SI values as the variables of obtained by alternate demonstration of the Lüscher eight-color table (SI 1) on the eyetracker screen, for the assignment for mathematics from the USE demo version (SI 2), the USE form (SI 3) and phrase “good mood” (SI 4) and the final USE mark of the respondents. The indicated factor structure of the correlation relationships demonstrates that the nature of the response to stimuli associated with past examinations in the respondents does not depend on the degree of their success. It also follows from the table that the similar pattern of the response is observed when presenting the eight-color Lüscher table and phrase “good mood” on the eyetracker screen. Responding to the presentation of the assignments in mathematics from the USE demo version and an USE standard form is an independent factor.

During the post-test interviews more than a third of respondents have noted that a strong destabilizing factor is teachers and parents’ statement that they doubt about the students’ ability to successfully pass the upcoming USE examination. Very often such kind
of doubts has been expressed by those respondents for whom it was typical to combine their intention to prepare their exam work free of errors and the desire to do any work as quickly as possible. Moreover, according to the respondents’ statements, in many schools not enough attention is paid to preparing students for the procedure of passing such examinations. This fact is the most alarming thing for those types of the respondents, which are characterized by a combination of low self-esteem, lack of self-confidence and high self-control.

Conclusions

The obtained results have confirmed the validity of our assumption that PC-assisted cardiograph Cardiocode and modern portable GP-3 type eyetracker (eyetracker) allow assessing the psycho-physiological component of the students’ conditioning/readiness for examination. During the confirmation of this hypothesis, we have also obtained statistically significant data that makes it possible to state that the mandatory part of preparation for examinations should be not only a subject-related training, but also a psychological conditioning of students targeted at improving their general stress tolerance and their emotional stability. An important part of such conditioning/preparation is also an educational activity, aimed at creating and strengthening the integrity of students, their fairness, increasing of their readiness to undertake the role of individuals solving vital problems. Versions of such conditioning/preparation, techniques and mechanisms included therein are described in detail in our papers [1, 2, 7, 14]. Within the framework of such conditioning activities, it is required to form skills of the control and regulation of their psychophysiological state in students. Particular attention should be paid to cultivation of capabilities of applying such skills in real daily practice in students.

The obtained experimental evidence has shown that transitions from a low level of psychophysiological conditioning of the students for their examinations to the respective high level thereof is really accompanied by significant changes in the organism performance, first of all, in the performance of the heart. Therefore, a reliable marker of such changes is the heart rate variability assessment using the Baevsky stress index (SI), as well as the oculometric peculiarities of response to the visual stimuli, which students associate with the upcoming examinations.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

References

Personal profile of systemic hemodynamics in solving global problems of public health

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Abstract
The study of systemic hemodynamics has been conducted in individuals who suffer from arterial hypertension. Regularities of formation of the personal profiles of the systemic hemodynamics have been determined in this category of patients. A fresh method of antihypertensive therapy is offered which is based on establishment of relationship between the personal profile of the systemic hemodynamics and the hemodynamic drug effect. The clinical effectiveness of the proposed method has been proven.

Keywords
Arterial hypertension, Metabolic syndrome, Systemic hemodynamics, Antihypertensive therapy, Volume compression oscillometry

Imprint

In 2018 the new guidelines of the European Society of Cardiology and the European Society “ESC/ESH Clinical Practice Guidelines for the Management of Arterial Hypertension” (hereinafter referred to as the Guidelines) to govern the treatment of arterial hypertension (hereinafter: AH) came into force. The new revised edition of the document is substantially different from the previous one; proposed is a fundamentally new variant of the initial therapy of AH: instead of a single drug therapy it is recommended now to begin the treatment immediately with the use of a two-drug combination. Selection of the drug combination, as it has been the case before, is based on the presence of diseases associated with AH, as well as the state of the hypertension-mediated organs, i.e., the organs involved in pathophysiological processes caused by AH. The Guidelines’ developers present a variety of different strategies to initiate and escalate BP-lowering medication to improve BP control rates initiating treatment with different monotherapies and then sequentially adding other drugs until BP control is achieved almost as a fundamental solution of the AH problem, but at the same time they complain that “Despite this, BP control rates have remained poor worldwide”. The strategy developers believe that ”bad” doctors should bear responsibilities for the stated inadequacy: they are those who are afraid of prescribing the proper dosage of the medical drugs and who are incapable of controlling BP medication; at the same time it is considered that patient adherence to treatment is low so that not all of them complete the course of their medication in full [1].

The effectiveness of the strategic approaches is treated in the Guidelines casually; in the opinion of the developers, there is a forceful argument in favor of the Guidelines’ correctness: “The evidence from RCTs demonstrating that BP control can be achieved in most recruited patients, and that no more than 5 – 10% of these patients exhibit resistance to the selected treatment regimen, suggests that ineffective drug therapy is not the source of the problem.”[1] (i.e. we, the strategy developers, escape our responsibility). In other words, if you have competent physicians and an eligible patient’s adherence, you can rise the efficacy of the AH treatment up to 90-95%!

Among the other things, the mere proposal to double the amount of the used drugs is an evidence for
an inefficacy of the conceptual approaches offered by them thereto. It is not the way to base the treatment strategies on taking into account comorbidities, when selecting the medication lines, since there are no accompanying diseases at the first stage of treatment; the target organs are not yet affected by the AH disease at the first stage; the presence of some associated clinical conditions points to a highly neglected disease case. In the meantime, in the scientific debates "hypertension remains the major preventable cause of cardiovascular disease (CVD) and all-cause death globally"; so that searching for fresh solutions to this problem is perhaps the most topical challenge for modern medicine [1].

Aims

The aims of our studies are systematization and applications of hemodynamic patterns in the diagnostics and treatment of AH.

Every medical student knows the following formula: 

\[ AP = CO \cdot TPVR, \]

where AP is an arterial pressure; CO is cardiac output; TPVR is total peripheral vascular resistance [2].

Taking into account the fact that the CO is the product of the stroke volume (SV) by the heart rate (HR), i.e. \( CO = HR \cdot SV \), the AP value is directly dependent on three key factors: HR, SV and TPVR. By influencing these parameters, the level of AP can be controlled, both upwards and downwards. The only thing is to identify the relevant treating factors. This truth is so simple that it is really surprising why it has not been so far used as the primary conceptual approach to the treatment of AH, as well as arterial hypotension. But, unfortunately, there is even no attempt to discuss this conceptual assumption at all. This is much stranger, since the effect of antihypertensive drugs (AHD) on the systemic hemodynamics (SHD) is a well studied subject; the evidence data are directly available, including annotations to drugs (see Table 1 herein).

The only justification is that, until recently, the "gold standard" in SHD studies has been the Swan-Ganz pulmonary artery catheterization, which implies an insertion of a special catheter into one of the main branches in the pulmonary trunk. Such procedure is not safe; 2-3% of cases are complicated by serious disturbances in the heart rhythm and conduction that hinders the widespread use of the method, even under the in-hospital conditions [3].

At present, the above mentioned drawback has been removed; moreover, appeared are accessible and, most importantly, non-invasive techniques for investigating SHD, which reveal vast prospects for their use in general medical practice [4].

Materials and methods

The materials of our studies cover 1447 examinees aged from 18 to 89 (mean age 37.5 years), including 832 (57.5%) males and 615 (46.5%) females.

Our method of examination is the compression oscillometry: for this purpose, we have used device KAP TsG oGom “GLOBUS” (Manufactured by Globus Ltd., Registration Certificate No. RZN2017/6582 dd. December 15, 2017), which allows non-invasively measuring 22 SHD parameters, including systolic arterial pressure (SAP), diastolic arterial pressure (DAP), HR, SV and TPVR. Since the values of SV and TPVR depend on the patient’s height and weight and do not have clear standard boundaries, in our calculations we used their integral analogues: SI (stroke index), calculated as \( SV/T \) where \( T \) is a human body surface area (m²), and SPVR (specific peripheral vascular resistance) equal to \( TPVR/T \). The standard SI value is 30-45 ml/m², and the standard SPVR parameter is 32 ± 6% arbitrary units. It is assumed that the normal values of HR, SAP and DAP are as follows: HR 60-80 beats per min., SAP 120-130 mm Hg, DAP 70-80 mm Hg.

Results

Results obtained from our studies are given further below.

In the above examinees we have revealed various combinations of HR, SI and SPVR parameters; we have pooled them to form 15 SHD profiles. In this case, noteworthy is the detected dependence of each profile on the corresponding AP level (see Table 2 herein).

The following SHD profiles have not been detected in any examinee: 111, 131, 132, 133, 232, 233, 312, 313, 323, 331, 332 and 333. Besides, in patients with increased SAP and DAP we have never recorded the SHD profiles as listed below: 213, 223, and 322.

<table>
<thead>
<tr>
<th>Group</th>
<th>SAP</th>
<th>DAP</th>
<th>HR</th>
<th>TPVR</th>
<th>SV</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>CCB</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>TD</td>
<td>↓</td>
<td>↓</td>
<td>←</td>
<td>↓</td>
<td>←</td>
</tr>
<tr>
<td>ACEi</td>
<td>↓</td>
<td>↓</td>
<td>←</td>
<td>↓</td>
<td>←</td>
</tr>
<tr>
<td>ARB</td>
<td>↑</td>
<td>↓</td>
<td>←</td>
<td>↓</td>
<td>←</td>
</tr>
</tbody>
</table>

*Legend: BB - beta-blockers; CCB - calcium antagonists; TD - thiazide diuretics, ACEi - ACE inhibitors, ARB - angiotensin receptor blockers; ↑ - increase, ↓ - decrease, ← - no effect available.
Table 2. Dependence of SHD profile on AP level

<table>
<thead>
<tr>
<th>SHD* profile (HR/SPVR/SI)</th>
<th>All</th>
<th>AP&lt;120</th>
<th>AP120-130</th>
<th>AP&gt;140</th>
<th>AP&gt;160</th>
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<tr>
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<td>3.9</td>
<td>4.8</td>
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<td>0</td>
<td>2.7</td>
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<tr>
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<td>12.5</td>
<td>10.4</td>
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<td>18.1</td>
<td>14.3</td>
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<td>4.8</td>
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<td>1.3</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Notes: SHD profile is ratio HR / SPVR / SI, where 1 - increased value of the parameter; 2 - normal value of the parameter; 3 - decreased value of the parameter.

123 and 211 SHD have not been found in the hypotension patients. The combination of the normal values of HR, SI and SPVR (SHD profile 222) occurred in 16.4% of the patients (see Figure 1 herein).

It would be logical to expect the prevalence of SHD profile 222 among the examinees with the normal levels of SAP and DAP. Indeed, in this category of examinees SHD, profile 222 occurs more often (22.9%), though not as often as one would expect. The above phenomenon may indicate only the following: AH is not only (and not as much as) an increase in AP. Early pathological manifestations of the AH disease in the form of impaired cardiac reflex activity and vascular tone imbalance for a long time are compensated by the redistribution of the hemodynamic constants. AP is the main hemodynamic parameter in the organism.
that provides normal perfusion; its stability guarantees an adequate blood supply to tissues; all compensatory hemodynamic responses are aimed at maintaining the normal AP level. The relatively rare occurrence of the normal hemodynamic profile is an indication of the completed compensatory hemodynamic responses at the early stages of AH.

The obtained data confirm the given concept: the normal SHD profile is almost absent in the patients with DAP> 90 mm Hg (0.9%); the profile has not been observed in the patients with SAP>152 mm Hg. All this clearly indicates that the exhaustion of the compensatory SHD mechanisms appears with grade 1 arterial hypertension.

In contrast thereto, in the patients with a decreased SAP (SAP <120) the normal SHD profile has been recorded 2 times more frequently (39%) than in those with the normal SAP. In our opinion, the logical explanation of this phenomenon is that a reduction in SAP is one of the earliest compensatory mechanisms of the response to an increase in the CO and TPVR parameters (see Figure 2 herein).

Among the examinees aged 18-25 years, a separate group is formed with healthy individuals according to their anamneses having the normal AP (n = 144). In the above category, only every fifth examinee (19.4%) has shown SHD profile 222 that is consistent with the previous results and gives us a reason to believe that hemodynamic disorders found prior to developing AH are formed well in advance before the first episodes of the abnormal AP increase [5].

The most frequently recorded case among the individuals with the normal SAP is SHD profile 212 (25.3%); less often found is SHD profile 221 (19.3%); every tenth (9.6%) has been reported to have SHD profile 122. The above distribution indirectly characterizes the polymorphism of the starting mechanisms in hemodynamic disorders preceding hypertension: in a third of patients (28.9%) the disorders start with increasing CO (SHD profile 221 and 122), and in every fifth individual (SHD profile 212) they begin with increasing TPVR (see Figure 3 herein).

A redistribution of the SHD profiles is a mandatory attribute of AH; at the same time, hemodynamics may change either according to the hyperkinetic type, which is characterized by an increase in the performance of the cardiac pumping activity (SV, HR), or in line with the hypokinetic type (distinguishing feature is the preferential growth of TPVR) or in accordance with the eukinetic type, when the values of all three parameters are in the middle of the oscillation range. At the onset of the disease, as a rule, the hyperkinetic hemodynamics prevails, while at its later stages the hypokinetic type is dominant [6, 7].

The obtained evidence data support the specified pattern regularity: in the patients with higher SAP observed is a tendency towards CO decreasing, while the share of individuals with an increased TPVR is directly proportional to the level of SAP (see Figure 4 herein).

Depending on the ratio between CO and TPVR, the SHD profiles are integrated by us in 3 groups: the hyperkinetic group (122, 221), the eukinetic group (222, 211, 321, 112, 113, 121, 123) and the hypokinetic group (311, 212). The relationship between the different SHD forms and SAP is shown in Figures 5, 6 and 7 herein.

Among the most common hyperkinetic SHD profiles, recorded has been profile 122; among the eukinetic profile types we have detected SHD profile 123; and among the hypokinetic profiles we have identified SHD profile 311.

**Conclusions**

The obtained results show that even in a healthy individual with the normal AP levels recording of a SHD physiological profile, which is characterized by the normal levels of CO and TPVR, is the exception rather than the rule. The share of individuals with impaired performance parameters CO and TPVR aged 18-25 years (80.6%) approximately correlates with the prevalence of AH among the individuals older than 60 years (80.7%). This correlation allows us suggesting that the AH onset should be related not to the age 40-50, as it is generally accepted, but much earlier life spans. It can be supposed that the hemodynamic disorder of this sort at the age of 25 may predict the onset of arterial hypertension with 60!

Latest research shows a close relationship between hypertension and the metabolic syndrome. It is believed that hyperinsulinemia and hyperleptinemia developing against the background of visceral obesity, associated with metabolic syndrome, contribute to an increase in CO and TPVR, thereby triggering the pathophysiological mechanisms of AH [8].

Knowing the SHD personal profile, we can select the proper AHD, taking into account its targeted effect on each component of the hemodynamics profile (see Table 3 herein).
Table 3. Effects produced by AHD on SHD

<table>
<thead>
<tr>
<th>AHP</th>
<th>Registration No. (SRMP)</th>
<th>HR</th>
<th>TPVR 1</th>
<th>TPVR 2</th>
<th>SV</th>
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<tr>
<td>Atenolol</td>
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<td>decrease</td>
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<td>decrease</td>
<td>decrease</td>
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<td>Bisoprolol</td>
<td>ЛП-004617-251117</td>
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<td>increase</td>
<td>decrease</td>
<td>decrease</td>
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<td>decrease</td>
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<td>Nevibolol</td>
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<tr>
<td>Metoprolol</td>
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<tr>
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<tr>
<td>Diltiazem</td>
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<tr>
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<td>decrease</td>
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<td>no change</td>
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<td>Indapamide</td>
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<td>no change</td>
<td>decrease</td>
<td>decrease</td>
<td>no change</td>
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</table>

Legend: HR - heart rate; TPVR1 - total peripheral vascular resistance in the first month of starting treatment; TPVR2 - total peripheral vascular resistance after a month of starting treatment; SI - stroke index.
### Table 4. AHD effects made on SHD

<table>
<thead>
<tr>
<th>AHD group</th>
<th>AHD</th>
<th>Effect by AHD* on SHD (Code)</th>
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<tr>
<td>Calcium antagonists</td>
<td>Nitrendipine</td>
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</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td>313</td>
</tr>
<tr>
<td></td>
<td>Diltiazem</td>
<td>112</td>
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<td></td>
<td>Amlodipine</td>
<td>212</td>
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<tr>
<td>ACE inhibitors</td>
<td>Perindopril, Enalapril</td>
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<tr>
<td></td>
<td>Zofenopril, Kaptopril, Chinoopril, Lizinopril, Ramipril, Fosinopril</td>
<td>212</td>
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<tr>
<td></td>
<td>Betaxolol</td>
<td>111</td>
</tr>
<tr>
<td>Betablockers</td>
<td>Nevibol</td>
<td>112</td>
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<tr>
<td></td>
<td>Atenolol, Bisoprolol, Metoprolol</td>
<td>141</td>
</tr>
<tr>
<td></td>
<td>Losartan</td>
<td>113</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>Valsartan, Candesartan, Eprosartan, Irbesartan, Telmisartan</td>
<td>212</td>
</tr>
<tr>
<td>Selective imidazoline receptor agonist</td>
<td>Moxonidin</td>
<td>212</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Dichlotazide, Indapamide</td>
<td>212</td>
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### Table 5. AHD selection priority

<table>
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<th>Order of priority in AHD selection</th>
<th>Characteristic</th>
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<tr>
<td>1</td>
<td>Normalizing improperly changed (increased or decreased) parameters, not affecting the normal levels</td>
</tr>
<tr>
<td>2</td>
<td>Normalizing improperly increased parameters, but decreasing the normal parameter</td>
</tr>
<tr>
<td>3</td>
<td>Normalizing improperly increased parameters, not affecting the decreased parameter</td>
</tr>
<tr>
<td>4</td>
<td>Normalizing improperly decreased parameters, not affecting the normal parameter</td>
</tr>
<tr>
<td>5</td>
<td>Normalizing improperly decreased parameters, decreasing the normal parameter</td>
</tr>
<tr>
<td>6</td>
<td>Normalizing one of the parameters, not affecting the other two</td>
</tr>
<tr>
<td>7</td>
<td>Normalizing one of the parameters, not affecting the other one and decreasing the normal value of one more parameter</td>
</tr>
<tr>
<td>8</td>
<td>Normalizing one of the parameters, not affecting the other one and increasing the normal value of one more parameter</td>
</tr>
</tbody>
</table>

### Table 6. AHD rating corresponding to individual SHD profiles

<table>
<thead>
<tr>
<th>SHD* profile HR/SPVR/SI</th>
<th>AP &gt; 140</th>
<th>AP &gt; 160</th>
<th>AP &gt; 170</th>
<th>Code and rating for AHD administration**</th>
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<tbody>
<tr>
<td>112</td>
<td>17.6</td>
<td>3.6</td>
<td>0</td>
<td>112, 111, 141, 212, 113</td>
</tr>
<tr>
<td>113</td>
<td>5.2</td>
<td>0</td>
<td>0</td>
<td>113, 112, 213, 212</td>
</tr>
<tr>
<td>121</td>
<td>0.7</td>
<td>4.5</td>
<td>2</td>
<td>111, 141, 212, 112</td>
</tr>
<tr>
<td>122</td>
<td>15.3</td>
<td>0</td>
<td>0</td>
<td>112, 141, 111, 212, 113, 213</td>
</tr>
<tr>
<td>123</td>
<td>1.1</td>
<td>0</td>
<td>0</td>
<td>113, 112, 213, 212</td>
</tr>
<tr>
<td>211</td>
<td>11.8</td>
<td>12.5</td>
<td>10.4</td>
<td>111, 212, 112</td>
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<tr>
<td>212</td>
<td>4.5</td>
<td>32.1</td>
<td>37.6</td>
<td>212, 112, 111, 141, 213</td>
</tr>
<tr>
<td>221</td>
<td>18.1</td>
<td>14.3</td>
<td>8.3</td>
<td>111, 212, 112</td>
</tr>
<tr>
<td>222</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>212, 112, 111, 141, 213, 312</td>
</tr>
<tr>
<td>311</td>
<td>7.1</td>
<td>18.7</td>
<td>22.9</td>
<td>212, 312</td>
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<tr>
<td>321</td>
<td>11.2</td>
<td>14.3</td>
<td>18.8</td>
<td>312, 312</td>
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</table>

*The SHD profile is ratio HR/SPVR/SI, where 1 - increased value of the parameter; 2 - normal value of the parameter; 3 - decreased value of the parameter.

** AHD Code - effect produced by AHD on HR/SPVR/SI, where 1 - decreasing the parameter; 2 - not affecting the parameter; 3 - increasing the parameter.
The mapping between the SHD profile and the AHD actions and effects on SHD is implemented by assigning a three-digit code (Code) to each drug; the first item of the Code exhibits the effect of AHD on HR (1- HR decrease, 2 - no effect, 3 – HR increase); the second item of the Code indicates the effect made by AHD on TPVR (1- TPVR decrease, 2 - no effect, 3 – TPVR increase 4 – increase of the parameter in the first month, and decrease therein after a month, etc.); the third Code item marks the effect produced by AHD on SV (1- SV decrease, 2 - no effect, 3 – SV increase) (see Table 4 herein).

The priority in selection of AHD definitely depends on the degree of its modulating effect produced on an individual SHD profile. Selected should be such a medical drug which is capable of normalizing improperly changed (increased or decreased) parameters of HR, SV and TPVR, but not affecting the SHD values remaining within the normal range. Characteristics of medical drugs of the second and next order of the priority are summarized by Table 5 herein.

Having identified the correlation between the individual SHD profile and the respective AHD, we can determine the rating modulating effect of the drugs on each SHD profile (see Table 6 herein).

Conclusions
1. Hemodynamic disorders appear at the preclinical stage of AH, well in advance (perhaps several decades) before the first recorded AH episodes.
2. In patients with increased AP, 15 variations of the SHD profiles are identified.
3. A hemodynamic effect of each AHD is determined by its pharmacodynamics as well as the patient's individual SHD profile.
4. Taking into account of an individual SHD profile is an additional criterion for the AHD selection to increase the efficacy of the treatment based on the above mentioned Guidelines. The given conclusion is based on the evidence data, which have been obtained by us earlier and which have demonstrated the effectiveness of this technology in nine times out of ten cases [9].

Statement on ethical issues
Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest
None declared.

Author contributions
The authors read the ICMJE criteria for authorship and approved the final manuscript.

References
1. The 2018 ESC / ESH Guidelines for the treatment of patients with hypertension.
The importance of the study of central hemodynamics using volumetric compression oscillometry in clinical practice: resolved and unresolved issues

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Abstract
The article discusses the promising possibilities of using the method of volumetric compression oscillometry in clinical practice, which allows to simultaneously determining 20 indicators of central hemodynamics. A comparative analysis with other research methods is presented herein, and the advantages of the presented method in the diagnostics of cardiovascular diseases are shown. The problematic issues in using this method and ways to solve them are considered herein.

Keywords
Central hemodynamics, Volumetric compression oscillometry, Cardiovascular diseases, Arterial hypertension

Cardiovascular diseases (CVD), according to the relevant WHO data, remain the leading cause of mortality worldwide. Arterial hypertension (AH) is considered as a separate disease and at the same time as a major risk factor for developing other cardiovascular diseases owing to its high occurrence rate and poor controllability, even in countries showing a high level of health care system functioning. The AH occurrence in the Russian Federation (in 2017) reached 39, 5% [1]. The risk of CVD-associated death doubles with every episode of surge of the systolic arterial pressure (AP) of 20 mmHg and the diastolic AP of 10 mmHg, from the starting level of 135/85 mmHg [2].

Despite the standardization to cover the AH diagnostics methods, the AH diagnosing in outpatient practice, especially at the initial stage of the disease, is a very difficult task. Rises in AP may be episodic, often at the time of the emotional, physical and stress-related overloads, while the normal AP in the same patients can be recorded at rest.

Thus, for example, some Polish researchers, basing on periodic examinations of 144 professional car drivers, middle-aged men 50.2 ± 9.3 years, have detected arterial hypertension in 39 individuals (27.9%). However, during the ambulatory arterial pressure monitoring daily, arterial hypertension was diagnosed in 104 of 135 persons (73.8%) [3].

Some other researchers, including Russian scientists, believe that under the influence of various factors, initially some parameters of central hemodynamics (CH) are changed, and that only thereupon a persistent, steady increase in systolic and diastolic AP appears, i.e., hypertension develops [4,2].

On the other hand, an administrated medication should take into account pathogenetic mechanisms of the AH development which may be as follows: a prevailing increase in stroke volume, in the peripheral vascular resistance or a combination of both factors. During the AH treatment "an escape effect" often develops, which is associated with the CH restructuring, so that the treatment becomes ineffective.

All the above evidence dictates the need for searching for a new approach to the tactics in the AH treatment and follow-up: in addition to systolic and diastolic pressure the CH parameters are to be taken into account. At the same time, required is continuous monitoring of the CH parameters, since a single
measurement thereof cannot detect abnormalities due to lability of the hemodynamic parameters. The CH examination is usually performed with ultrasound technique to image the heart (Echocardiography), which involves applications of sophisticated ultrasound equipment, trained personnel and takes a lot of time. In this connection, the ECHO CG cannot be considered as a method belonging to the family of the CH monitoring techniques, especially if this examination is carried out regularly under the ambulatory conditions.

Today this problem can be successfully solved with the use of device CH HSS osm GLOBUS, the hardware & software system designed and manufactured for noninvasive examination of central hemodynamics with the use of the method of volumetric compression oscillometry (VCO).

The problem of measurements of the main CH parameters in parallel with the use of a compact simple device has been first formulated in the framework of national Russian space mission programs. In order to provide medical monitoring of the cosmonauts’ health state under the conditions of long-term space missions, required has been design and development of original diagnostics devices. The offered hemodynamics monitoring equipment designed for this purpose by the experts of the Institute of Biomedical Problems and the Institute of Aerospace Medicine is based on the conceptual ideas and methods developed by N.N.Savitskiy, 1956. [5].

Oscillometric devices used by orbital stations "Salyut" and "Mir" have demonstrated their capabilities, which are completely equivalent to those available in an in-hospital functional diagnostics unit furnished with the respective equipment to record the main CH parameters. CH HSS osm GLOBUS has been commercially manufacturing by Globus LLC, Belgorod, Russian for the last 15 years (see Figure 1 herein).

The CH examination device is a medical instrument designed and manufactured for applications both by intuitive users and for examinations of in- and out-patients. The device is approved for the use by the Russian Federal Service for Health Supervision, validated, appropriately registered and certified; an appropriate Russian national Certificate of Conformity and Certificate of Product have been issued [6].

An assessment of the recorded CH parameters can be performed by an intuitive user at home or under the outpatient conditions with a simple method of arterial pressure measurement conducted with an upper-arm cuff oscillometric instrument, which is connected with a portable device capable of assessing pulse oscillations in the brachial artery walls under the conditions of rising pressure in the pneumocuff.

The received signal in the form of an oscillogram is subjected to analytical and mathematical processing, upon the results of which the major CH parameters are determined. An example of a hemodynamics data record is presented in Figure 2 herein. The obtained CH parameters can be divided by convention into 4 groups as follows:

1. Types of AP: systolic AP (SAP), diastolic AP (DAP), true systolic AP (TSP), mean AP (MAP), stroke AP (strAP is a difference between SAP and TSP), pulse AP (pAP), pulse AP velocity;
2. Vascular characteristics: linear blood flow velocity (LBFV), pulse wave propagation velocity (PWPV), vascular system compliance (VSC), total and specific peripheral vascular resistance (TPVR, SPVR);
3. Cardiac activity indices: cardiac output (CO), stroke volume (SV), cardiac and stroke indices (CI, SI), volumetric ejection rate (VER), left ventricular contraction capacity (LVCC), energy consumption per liter of blood circulation (EC);
4. Types of blood circulation: hyperkinetic, eukinetic and hypokinetic circulation types, differentiated by three characteristics as follows: SI, CI and TPVR.
Результаты исследования

Артериальное давление

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Сердечная деятельность

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<td>Ударный объем</td>
<td>лл 43</td>
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<td>5</td>
<td>Ударный индекс</td>
<td>лл/кг 23</td>
<td>30 - 45</td>
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<td>6</td>
<td>Объемная скорость выброса</td>
<td>лл/с 143</td>
<td>160 - 300</td>
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<tr>
<td>7</td>
<td>Мощность сокращений ЛЖ</td>
<td>ед/с 1.3</td>
<td>2.0 - 4.5</td>
</tr>
<tr>
<td>8</td>
<td>Расход энергии на 1 л СВ за минуту</td>
<td>ед/с 11.3</td>
<td>9.0 - 12.7</td>
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Сосудистые показатели

<table>
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<tr>
<th></th>
<th>Норма (рабочее)</th>
<th>Оценка</th>
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<tbody>
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<td>Скорость кровотока лин.</td>
<td>см/с 31</td>
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<tr>
<td>2</td>
<td>Скорость пульсовой волны</td>
<td>см/с 785</td>
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<td>Градиент давлений</td>
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<tr>
<td>5</td>
<td>Удельный перф. сосуд.</td>
<td>усл. ед. 31</td>
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*Условия применения нормативов: "в покое"

Осциллограмма

Гипотензия.
Гипокинетический тип гемодинамики. Изыточная прокходимость прекапиллярного русла.

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Тел/факс: 8-910-466-49-85
**Aims**

The aim of this study is to assess applicabilities and capabilities offered by device CH HSS osm, the hardware & software system for noninvasive examination of central hemodynamics with the method of volumetric compression oscillometry (VCO) in clinical practice on the basis of the relevant data evidence available in Russian national publications.

**Methods**


**Results**

1. Comparison and comparability of the CH parameters’ investigation results with other methods

Comparative characteristics of several methods of CH calculation are shown in Table 1 herein (the data evidence reported from http://gemodinamika.ru with supplements).

As seen from the above table, the advantages of the VCO method are as follows: noninvasiveness, rapid simultaneous measurement of 20 hemodynamic parameters, a simple automated procedure of measuring, its accessibility and availability to the population.

Published are several papers, where assessments of the central hemodynamics with the use of the CH HSS osm GLOBUS device employing the oscillometric methods are found to be in a good agreement with the results of other applicable methods applied to the hemodynamic examinations.

In the paper by V.A. Mazurok, 2017, compared have been the reproducibility of cardiac output indices measured by the classical technology of pre-pulmonary thermodilution and those calculated according to VCO using device CH HSS osm GLOBUS [7]. 200 parallel measurements have been recorded (100 measurements with each method) in 7 cardiac sur-

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Invasive method: thermodilution</th>
<th>Echocardiography</th>
<th>Oscillometry CH HSS osm GLOBUS</th>
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<tr>
<td>Accuracy of cardiac output calculation</td>
<td>High level</td>
<td>Medium level (KK = 0.86-0.9)</td>
<td>Medium level (KK = 0.85-0.9)</td>
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<td>Capability to measure actual values of the AP levels</td>
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<td>Available</td>
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<td>Methodology complexity of the method</td>
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<td>Low</td>
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<tr>
<td>Invasiveness of the method</td>
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<tr>
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<td>Low</td>
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<tr>
<td>Duration of the measurement procedure</td>
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<td>30 minutes and more</td>
<td>Less than 1 minute</td>
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<td>Available</td>
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<td>Requirements for medical staff training and qualification</td>
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<td>High (physician)</td>
<td>Medium level (nurse)</td>
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<td>Suitability of the method for screening</td>
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<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Stress test applicability</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Availability and accessibility to the population</td>
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<td>No</td>
<td>Yes</td>
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<tr>
<td>Specific requirements for the examination conditions</td>
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<td>Lying position</td>
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<td>Applicability of continuous automated monitoring</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Applicability of continuous automated monitoring</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*According to the data published on http://gemodinamika.ru with supplements*
surgery patients in their early post-operation period. The mean values of cardiac output parameters measured with thermodilution and VCO have been found comparable: $5.41 \pm 0.12$ vs. $5.33 \pm 0.13 \text{ l min}^{-1}$, respectively; cardiac index values of $2.93 \pm 0.13$ vs. $2.92 \pm 0.94 \text{ l min}^{-1} \text{ m}^{-2}$, accordingly. The mean error in CO and CI is approximately $10\%$. The author concludes that VCO may be used to calculate CO in cardiac surgery patients that is very important for this category of patients. When interpreting the obtained indices, the limitation for any method on the CO calculation, based on an estimation of the pulse wave, should be taken into consideration.

Comparable results have been obtained by V.A. Degtyaryov, 2015, by analyzing the CO data delivered with VCO and those produced with the thermodilution method in patients with acute myocardial infarction both during their scheduled examinations and under the conditions, when admitted to hospital [8]. For this purpose, a total of 70 investigation procedures have been completed. The CO value obtained using the thermodilution method has been recorded to be $4.986 \pm 0.222 \text{ l/min}$ versus $4.76 \pm 0.48 \text{ l/min}$ delivered with the VCO method, so that the correlation coefficient has been found to be $0.92$ [8].

In the paper by Trivozhenko A.B. et al., 2019, the expert Doppler echocardiography has been applied as the reference technology to assess the accuracy of the VCO method. The method has demonstrated an allowable accuracy in measuring SV ($\pm 15\%$), with consistent displacements ($\pm 1.96$ standard deviations) in the estimation to describe agreement between two quantitative measurements produced by two techniques according to the Bland-Altman plotting. A close correlation between the oscillometric peak blood flow velocity has been detected in the brachial artery and the Doppler velocity of the blood flow at the aortic mouth ($p <0.001; r = 0.85$). A similar correlation has been observed between the aortic Doppler spectrum integral and the peak arterial flow velocity measured with VCO ($p <0.001; r = 0.68$) [9].

Researchers S.Y. Ivanov and N.I. Livshits, 2015, have compared accuracy of arterial pressure measurements obtained with the auscultatory technique and the VCO method. For this purpose, 50 patients having hypotension, the normal pressure level and mild/moderate arterial hypertension have been tested. Daily blood pressure monitor "Kardiotechnika 04-AD3" (CJSC "INCART", Russia) has been used as the reference technique. In parallel with the automatic monitor pressure measuring, two experts have measured AP with the help of a dual phonendoscope according to the "blind" method assessing the first and fifth phases of Korotkoff sounds, reading the pressure digits in the cuff displayed on the device screen.

When using the oscillometric method, a more significant difference of -1.8 mmHg for SAP and 0.8 mmHg for DAP (SD 5.0 and 5.2 mmHg, respectively) has been observed. Thus, the arterial pressure measurement by the Korotkoff method delivers more accurate results than using the oscillometric method. However, in about 6% of patients the AP measurement by the Korotkoff tones seems to be more difficult due to the presence of hollow low-amplitude sound tones. The oscillometric method for this sort of patients appears to be more preferable. Thus, the accuracy may be higher with the simultaneous use of both methods [10].

In the paper by S.A. Shidlovskaya et al., 2015, it is shown that in case of a pronounced stage of AH (stage III) the degree of the overread SAP obtained with the auscultatory Korotkoff method is fairly greater than it is the case with that delivered by VCO. The VCO method has been found to be more accurate for this category of patients. The difference between the AP readings measured by the Korotkoff and those obtained with the VCO method is an indicator of a pronounced aortic wall and artery lesion and, consequently, a predictor of an unfavorable outcome in patients suffering from AH. The value of the difference between the AP readings measured by the Korotkoff and those obtained with the VCO methods demonstrates the degree of actual resistance and stiffness of the vascular system [11].

The paper by M.S. Gerashchenko et al., 2016, offers an analysis of basic errors typical to the oscillatory methods involving the use of the pneumatic compensation cuff, on the basis of the applied the circuit design techniques employed for development of measuring instrumentation by LabVIEW. Shown are the prospects for the use of the hydro-cuff technology to generate oscillations for assessing hemodynamic parameters as well as a possibility of implementing a new class of devices to solve the topical task of evaluating the CH hemodynamic parameters [12].

In the paper by Y.G. Kuzminski and S.V. Shilko [13], 2014, on the basis of a single-dimensional biomechanical model of hemodynamics, confirmed is an efficacy of the primary diagnostics of the cardio-
vascular system condition, using an original software, which implements a mathematical analysis of the relevant oscillometric data. The screening conducted with the proposed method allows extending the capabilities of classical oscillometry and obtaining important data on the state of the heart and the blood vessels, including assessments of adaptation capabilities in human subjects (in particular, athletes) under the conditions of different physiological loads.

2. Many works are devoted to the CH investigations with employing the VCO method in healthy subjects [14], adolescents under various climatic conditions [16], university students [17, 18] and athletes [19] aimed at identification of the adaptation abilities in the organism and the CVD prevention.

According to the data obtained by L.V. Shpak, E.S. Galoshina, 2013 presented in [14], when identifying the blood circulation type in normal subjects, with the mean age 27.8 ± 0.8 years, at an optimal and normal AP (118.5 ± 1.6 / 71.82 ± 1.2 mm Hg), more frequently (32%) recorded is the hyperkinetic type of blood circulation: SI 46.75±1.92, CI 3.5±0.05, TPVR 1112.25±23; then the eukinetic type (30%) follows: SI 39.6±1.6, CI 3±0.06, TPVR 1170.5±; and less frequent appears the hypokinetic type (24%): SI 36.2±2.5, CI 2,8±0.08, TPVR 1359.8±28.5, including the mixed type (14%): SI 44 ± 2.1, CI 3.5 ± 0.2, TPVR 1297 ± 44.4, that generally is consistent with the evidence data found in other studies [15].

L.I. Grechkina et al. in their investigations of systemic hemodynamics with application of the VCO method in male adolescents aged 13-16 in Magadan (n = 424) and Moscow (n = 437) offer their own classification of the following three types of the CH regulation: the cardiac type, the vascular type and the mixed (cardiovascular) type thereof. As to the cardiac type of the regulation, hemodynamics is maintained by increasing HR; under the vascular type of the regulation we can observe enhancing of the left ventricular contraction capacity and an increase in SV; the cardiovascular type involves both mechanisms as described above. The researcher believes that the most appropriate and well-balanced type of the systemic circulatory regulation are the cardiovascular and vascular types thereof.

Adolescents showing the cardiovascular type and especially the vascular circulation type have higher adaptation abilities of the cardiovascular system as compared to those with the cardiac type, when even at rest a higher level of HR is found that requires a constant consumption of the organism energy resources.

An analysis of the distribution of their hemodynamic indices according to the blood circulation self-regulation type have demonstrated that the cardiac type is observed in 63.7% of the Magadan's students and 44.4% of the Moscow's students, the cardiovascular type has been identified in 26.9 and 41.2% of the cases, and the vascular type has been detected in 9.4 and 14.4 % of the cases, respectively, referred to the total number of all surveyed adolescents.

The authors thereof arrive at a conclusion that there are significant stresses in the performance of the cardiovascular system and reductions of its adaptation capabilities upon a long-term exposure to unfavorable environmental factors in the Far North in Russia that may result in the development of cardiovascular diseases.

In the study tests in 368 young men, students, the natives of the North-East of Russia, with the mean age of 18.5 ± 0.08, an analysis of the distribution of the individual values of the systemic hemodynamics index types employing the VCO method has shown that 48.1% of the adolescents has the cardiac type of the blood circulation self-regulation, 35.9% of them has demonstrated the cardiovascular type and 16.0% of the cohort have the vascular type thereof. The highest values of SAP, DAP, SV, LVCC and TPVR are typical to individuals with the vascular type of the regulation, and the respective lowest values have been found to be typical to individuals with the cardiac type thereof. Male adolescents with the cardiovascular type of the blood circulation self-regulation have the medium-level indices. At the same time, the values of HR, PWV and the Kerdo vegetative index have been reported to be the highest in young men with the cardiac type, and the respective lowest parameters have been recorded for the young individuals with the vascular type. The author comes to a conclusion that adolescents with the cardiovascular type and particularly with the vascular circulation CH type have higher adaptation abilities of the cardiovascular system as compared to those showing the cardiac CH regulation type, who have even at rest a high level of HR values that requires an interrupted use of the organism energy resources [16, 17].
3. Possibilities of using the VCO method in identification of a cardiovascular risk, clarification of pathogenesis of arterial hypertension and other CVDs

In research papers by Strakhova N.V., et al., 2013, clearly confirmed is the possibility of using the hemodynamics assessment with the VCO method in identification of a cardiovascular risk. Based on the conducted mathematical analysis, the authors therein propose to include the VCO indices in the cardiovascular risk scoring system. According to the conventional CVD risk factors with assessing 14 VCO indices, designed is a point risk scale capable of predicting a high and very high cardiovascular risk. A significant relationship between the VCO indices and the clinical course of AH has been detected. The most important criteria for an assessment of cardiovascular risks are the level of AP, PWV, LBFV, SPVR parameters and the qualitative characteristics of an oscillogram ("a bulge"). The last parameter indicates an increased vascular rigidity.

An increase in the total score according to the newly proposed scale by more than 20 points with a sensitivity of 95.6% and a specificity of 65.6% makes it possible to predict the presence of a high and very high cardiovascular risk and contributes to an early identification of this category of patients followed by taking preventive and therapeutic measures [20,21] well in time.

The same researchers in their further works have analyzed changes in the hemodynamic status with the use of the VCO method in patients with AH combined with postinfarction cardiosclerosis that is of great importance in assessing the severity of the patient’s condition, prediction and specification of the required medication. Detected is a significant relationship between the VCO indices and the cardiovascular complication risk factors as well as the presence of the postinfarction cardiosclerosis. An increase in the PWV, LBFV, SAP VCO, MAP values and a decrease in the vascular compliance parameter, as determined by the VCO method, are predictors of an unfavorable clinical course of AH in combination with postinfarction cardiosclerosis [22,23].

Ovsyannikov V.V. et al, 2014, 2015, based on the application of the VCO method, have detected higher values of the MO, SV, TPVR, PWV, LBFV parameters and a low compliance of the vascular system in case of combination of type 2 diabetes with AH in comparison with a group of AH patients without diabetes. The authors thereof conclude that the variations in hemodynamics of the different grades, detected in a patient with type 2 diabetes accompanied by AH with the VCO method, have a common pathogenetic element, namely the insulin resistance, should be considered as early indicators of a disorder in the elastic properties of the aorta [24, 25].

In the paper by L.V. Shpak et al., 2013, we can find an evaluation of the evolution of hemodynamic parameters at the stage of the initial development of AH and at its further stages of increasing severity. Among the above indicators, TSP and MAP become the universal parameters as their recording is possible with the use of VCO only. The TSP dynamics serves as a possible pathogenic mechanism, which reflects the value of the pressure, to which the inner walls of the arteries is subjected under AH, that may be of a prognostic significance, and at the same time, it might be concluded that MAP can be a criterion for AH progression. The latter is particularly important because the MAP indicator is an integral value of all AP changes from the minimal to the true value, and this integral value is characterized by its significant constancy, when exposed to various stimuli, but demonstrates a reliable increase from AH grade 1 to grade 3 degree.

It is reported that in patients of AH grade 1 to 3 the vascular characteristics, the indicators of the cardiac activity are increased, while the vascular index, i.e. the vascular wall compliance, is decreased, that indicates the strengthening of the myocardial contractile function against the background of increasing the arterial walls tonic tension and the peripheral resistance in the resistive vessels. In this case, observed is a change in the formation of the cardiac hemodynamics types: the share of the hyper- and eukinetic types from AH grade 1 to grade 3 is decreased due to an increase in the occurrence rate of the mixed and especially hypokinetic variants thereof [14].

In another paper by the above mentioned authors an analysis of hemodynamics in patients with AH in their pre- and postoperative period is conducted. Regardless of the initial level, AP decrease occurs after surgery in all patients, but, in case of the corrected AP, it appears equally due to reducing the vascular and myocardial factor tension, and in case of the not corrected AP it takes place mainly due to the myocardial factor attenuation [26].
4. Papers devoted to the AH treatment based on AP monitoring data obtained with VCO

The scope of these papers deals with an evaluation of efficacy of the AH treatment with the VCO method. M.V. Lozhakova, 2008, has evaluated the efficacy of the AH monotherapy with bisoprolol [27]. E.V. Pravdintseva et al., 2011 have assessed hemodynamics when administering angiotensin converting enzyme inhibitor to prevent cardiotoxic effect during chemotherapy [28].

D.I. Emelyanova et al., 2014 have evaluated differentiated administration of antihypertensive therapy in 110 pregnant females considering their type of central hemodynamics identified with the VCO method. The researchers have arrived at a conclusion that an assessment of hemodynamics in pregnancy, against the background of AH, is urgently required. In the absence of a differentiated approach to estimating hemodynamics, pregnant females with AH receive non-justifiable antihypertensive therapy, which, under the hyperkinetic type, may provoke a disproportionate development of the fetus/newborn. Unreasonable antihypertensive therapy under the eukinetic hemodynamics type may cause placental insufficiency, and that under the hypokinetic type may lead to an insufficient fetal weight. Therefore, it is recommended to use the VCO method for the purpose of identification of the CH type and selecting the proper pathogenetically grounded antihypertensive therapy in pregnant females [29].

The research paper by R.V. Gorenkov et al, 2019, treats outpatient examinations in 126 human individuals (mean age 56.5 ± 3.7 years) with arterial hypertension. In accordance with the obtained initial hemodynamic data, the patients were administered with hypotensive agents of different groups: in case of an increase in SV: mainly selective beta-blockers; in case of an increase in TPVR: angiotensin converting enzyme inhibitors or angiotensin 2 receptor blockers or calcium antagonists; in case of an increase in both parameters: combination therapy. During such differentiated treatment, depending on hemodynamic parameters, in the majority of the patients (114 of 126, i.e. 90.5%) reported is a decrease in arterial pressure or reaching the target level thereof. The researchers conclude that hemodynamic monitoring with the VCO method allows providing a more accurate approach to the hypertension treatment and justify the proper selection of the required hypotensive drugs, as well as to adjust the treatment based on the pathogenetic mechanisms of the AH development [30].

It should be noted that despite an obvious advantage of the VCO method in early diagnostics of the disease and in selection of the proper justified medication therapy in AH patients, the scope of applications of the method remains unfortunately still not broad: VCO is mainly employed for the purpose of scientific research. It may be attributed to difficulties for a medical practitioner to assess twenty parameters of CH and make prompt decisions under limited time conditions scheduled for examination in outpatients.

A new approach to the issue of the AH treatment taking into account the hemodynamic data is presented by M.A. Yakushin, et al., 2017. The researcher has developed a PC-assisted expert system capable of making an optimal decision in selection of the most suitable hypotensive drug, considering the CH parameters obtained as a result from the examination with the VCO method. In addition to the considered CH parameters, the mechanism of action of a hypotensive drug, its side effects, patient’s age and comorbidities are taken into account. Based on the above, immediately upon completion of the examination procedure, the software of device CH HSS osm GLOBUS delivers automatically recommendations on what specific drug can be administered by the doctor. This makes it possible to widely introduce this method in clinical practice, namely in an ambulatory health care unit.

Clinical efficacy of the proposed method has been confirmed for a cohort of 272 elderly patients (aged over 60) [31].

There are also some other features of the VCO use in the CH assessment. This sort of examinations should be carried out on a regular basis in order to accurately identify a tendency in CH in an examined individual. Besides, it should be mentioned that in the treatment of AH the phenomenon of "escape" from hypotensive therapy appears. SHD monitoring allows avoiding these phenomena and conducting an adjustment of medication therapy well in time. A solution to this problem can offer telemedicine. Proposed is an automated systematic monitoring of CH indices recorded either at home or in ambulatory with further transfer of the recorded data to a specialized medical organization responsible for data accumulation, processing, storage and continuous analysis thereof with periodicity identified for each patient individually or as emergency measures.
The use of telemedicine and specialized medical PC-assisted instrumentation systems allow medical staff to support and monitor the health state in their patients remotely [31, 32, 33].

Conclusions

The conventional arterial pressure measurement is not capable of delivering data on the mechanisms of the AH development, detecting early stages in the AH progression and predicting efficacy of hypotensive drug therapy and development of refractoriness to hypotensive therapy. In this regard, administration of an adequate drug therapy on the basis of the central hemodynamics indices determined with the VCO method in dynamics would be treated as a more accurate technique, which properly takes into account the pathogenetic mechanisms of the AH development, capable of achieving the specified targets and reducing CVD mortality.

Research summary

1. The investigation of central hemodynamics with the VCO method is comparable with the generally accepted invasive technique and some other methods of central hemodynamics examinations.
2. The use of VCO is acceptable and reasonable provided that multiple VCO examination procedures are completed, since the hemodynamic parameters are labile.
3. The VCO method for assessing the central hemodynamics can be used for prediction of a cardiovascular risk under various human individual conditions: pregnancy, physical loads in athletes, anesthesia in case of surgery, comorbidities like arterial hypertension, diabetes, postinfarction cardiosclerosis etc.
4. The CH examination employing VCO makes it possible to adequately select the proper drug therapy, considering the identified type of blood circulation, and adjust the medication, if required.
5. Due to the complexity of the CH data interpretation, for the purpose of a wide application of VCO in clinical practice, a new software, capable of delivering assessed results and findings, should be developed.
6. To extend the scope of the applications of VCO in clinical practice it is necessary to involve capabilities and possibilities offered by telemedicine, which enable physicians to advise patients remotely, provide remote monitoring of their health status, and adjust their treatment, if required. It is especially applicable to elderly and disabled patients.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

References

hardware and software package for noninvasive study of central hemodynamics by volume compression oscillometric. Information and telecommunication technologies. 2017; S: 41-5. [in Russian]

Cardiometric evidence data on human self-control of emotional states in the context of the use of metaphoric associative cards

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Abstract
The paper presents our experimental evidence of validity of our hypothesis that definite, substantively different, psychophysiological states of a human individual can be really fixed with the use of metaphoric associative cards, and that transitions from one psychophysiological state to another are accompanied by significant changes in the performance of the human organism, and, first of all, in the performance of the heart. It has been shown that the metaphoric associative cards can serve not only as a good forecasting tool, a sort of predictors of human behavior in certain emotionally charged, stress-provoking, situations, but also as a means for active modeling of optimal mode to adequately overcome these difficulties.

Keywords
Cardiometry, Heart rate variability, Baevsky stress index, Emotional state, Validity, Coaching associative cards, Metaphoric associative cards, Psychocorrection, Psychotherapy, Psychological consultation, Stress, Subjective genesis, Supra situational activity, Psychosomatic self-regulation

Introduction
Metaphoric associative cards have been included for a long time in the repertoire of diagnostic and therapeutic means used by coaches and practical psychologists. The number of various sets of metaphoric associative cards grows rapidly. Observed is an increase in the frequency rate and variety of training courses aimed at their application.

But until now, no systematic studies related to tracing and assessments of psychophysiological responses in testing with the use of metaphoric associative cards have been conducted. The existence of such responses follows from an assumption that due to the associations, actualized by such cards, certain cognitive and affective components of the individual’s life experience begin “to awake” in the tested human subjects. For example, such mobilization can be manifested in a certain pattern of the cardiovascular system performance. If the idea of such associations is not only a theoretical construct, and if, with the use of metaphoric associative cards, some definite, substantively different, psychophysiological states of a human person are really fixed, then the transitions from one emotional state to another are accompanied by significant changes in the performance of the human organism, and, first of all, in the performance pattern of the heart. Taking into account the results of our previously described studies [1-3, 8-11], it can also be assumed that such changes can be recorded by assessing heart rate variability using the Baevsky stress index (SI).

Materials and methods

To verify the hypothesis formulated by us above herein, we have completed a series of experiments, in which various emotional states generated due to facing different life difficulties have been modeled with metaphoric associative cards. The psycho-physiological responses corresponding to these states have been recorded using PC-assisted hemodynamic analyzer Cardiocode. Besides, we have taken into account the results of our previous experiments, which confirm that an increased, in comparison with average values, Baevsky stress index (SI) can be considered as a fingerprint of the sthenic response to a stimulus, and a reduced value thereof can be treated as a fingerprint of the asthenic response to a stimulus [1-3, 8-11]. We also have considered that just the SI values are more effec-
tive for the purpose of the evaluation of the person's emotional response nature than changes in the human individual's heart rate [1-3, 10].

Standard metaphoric associative cards of Moritz Egetmeyer (Moritz Egetmeyer OH-Cards) and some other sets of coaching associative cards created by I. Shmelev and S. Gracheva have been used in our experiments. This choice has been made considering the widespread long-term practice of the effective use of precisely these sets of metaphoric associative cards by consultants and psychotherapists of various profiles as well as taking into our successful experience in the use of these sets in evaluating the psychophysiological consistency, when analyzing various ego states [2, 8].

Our study has covered 105 respondents (with an average age of 21, the standard deviation was 4.5 years in the sample as a whole). The same algorithm for the work of all respondents has included the sequential execution of the tasks as described below. To start with, respondents have been asked to select metaphoric cards, which they associate with the following emotional states:
1) highest unreadiness/worst conditioning for an important exam; 2) highest readiness/best conditioning for an important exam; 3) highest unreadiness/worst conditioning for an important examinations period; 4) highest readiness/ best conditioning for an important examinations period; 5) highest unreadiness/ worst conditioning for any important life's trial; 6) highest readiness/ best conditioning for any important life's trial.

To illustrate this, some of the variants of metaphoric cards most often selected by the respondents to indicate their negative and positive emotional states are given in Figure 1 herein.

Upon presentation of the cards, each respondent for 15 seconds alternately fixed his attention on those cards, which he/she associated with each of the above emotional states. The next task (No. 7 according to the testing procedure) for each respondent was to select all the metaphoric cards that he/she associated with his/her positive emotional states, referred to the highest readiness/best conditioning for an important exam, an important examination period, for any important life's trial, and thereupon to fix his/her attention on all such cards for 15 seconds in parallel. The final task (No. 8 according to the testing procedure) for each respondent was to focus his/her most possible attention to a freely swinging pendulum on a tripod and to how the pointed part of the pendulum weight drew elliptical trace designs in sand at the pendulum's bottom.

When performing the above tasks, cardiograms in the examinees were recorded using PC-assisted hemodynamic analyzer Cardiocode. Upon completion of the recording, utilizing original specific algorithms of the Cardiocode software, values of the Baevsky stress index (SI) were calculated for each examinee.
The statistical analysis of the obtained data has been performed using statistical package STADIA 8.0.

Results and discussion

The obtained statistical patterns in determining the SI values for various emotional states in the respondents are presented in Table 1 herein.

The first column in the present and all the following tables shows the numbers to indicate the following emotional states, which appear, when the respondents have fixed their attention:
1) on those metaphoric cards, which are associated with their highest unreadiness/worst conditioning for an important exam;
2) on those metaphoric cards, which are associated with their highest readiness/best conditioning for an important exam;
3) on those metaphoric cards, which are associated with their highest unreadiness/ worst conditioning for an important examination period;
4) on metaphoric cards, which are associated with their highest readiness/ best conditioning for an important examination period;
5) on metaphoric cards, which are associated with their highest unreadiness/ worst conditioning for any important life's trial;
6) on metaphoric cards, which are associated with their highest readiness/ best conditioning for any important life's trial;
7) on all simultaneously considered metaphoric cards, which are associated with their highest unreadiness/ worst conditioning for any important life's trial;
8) on the freely swinging pendulum on a tripod and on how the pointed part of the pendulum weight draws elliptical trace designs in sand at the pendulum's bottom.

The static significance of differences in mean values was confirmed using the χ criterion (chi-square), which, as noted above, has been assessed using statistical package STADIA 8.0.

To identify a latent structure of the obtained data collection, a factor analysis has been conducted. Besides, it has been also taken into account that the distribution of the calculated indicators of the heart rate variability SI values differ from the Gauss-Laplace distribution. Therefore, in order to identify the correlation relationships, we have used the Spearman rank correlation and the Kendall concordance coefficients. Since the nature of the identified relationships for each of these coefficients is similar, the data for the Spearman coefficient are given by us herein only because of greater generality of the latter.

The factor analysis has been performed by calculating the correlation matrix of the major components with their further rotation to obtain the simplest interpretable factor system, based on the STADIA 8.0 statistical package developer’s recommendations [4]. At the same time, the major axes of the ellipse of analyzed objects’ scattering, eigenvalues of which are greater than 1, have been taken into consideration as the main components. For the purpose of an interpretable description of the factors, marker variables have been utilized, which provide for a meaningful interpretation of their possible nature. In doing so, the variables with a high interrelationship with a given factor exactly have been chosen as the above variables.

In our explorative factor analysis, conducted has been a step-by-step reduction of the number of the main components, followed by Varimax rotation for formulating a hypotheses on the optimal factor structure of the studied latent relations. The obtained data allowed suggesting that, as shown in Table 2 herein, the optimal structure should include 4 factors.

During the confirmatory factor analysis, in order to verify the hypothesis for the optimal factor structure in the studied latent relations, a more detailed calculation of factor loadings, reflecting their geomet-

<table>
<thead>
<tr>
<th>Ego-states</th>
<th>Arithmetic mean</th>
<th>Standard deviation</th>
<th>Median</th>
<th>Asymmetry</th>
<th>Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>429</td>
<td>378.6</td>
<td>290</td>
<td>2,019</td>
<td>8,042</td>
</tr>
<tr>
<td>2</td>
<td>292,1</td>
<td>209.8</td>
<td>231</td>
<td>1,286</td>
<td>4,589</td>
</tr>
<tr>
<td>3</td>
<td>343,9</td>
<td>276.2</td>
<td>262</td>
<td>1,874</td>
<td>7,926</td>
</tr>
<tr>
<td>4</td>
<td>298,7</td>
<td>250.8</td>
<td>223</td>
<td>2,163</td>
<td>8,904</td>
</tr>
<tr>
<td>5</td>
<td>330,7</td>
<td>260.1</td>
<td>290</td>
<td>3,141</td>
<td>19,3</td>
</tr>
<tr>
<td>6</td>
<td>273,7</td>
<td>234.4</td>
<td>199</td>
<td>2,21</td>
<td>9,143</td>
</tr>
<tr>
<td>7</td>
<td>242,1</td>
<td>166.4</td>
<td>204</td>
<td>1,419</td>
<td>5,453</td>
</tr>
<tr>
<td>8</td>
<td>276,7</td>
<td>198.7</td>
<td>256</td>
<td>1,319</td>
<td>4,555</td>
</tr>
</tbody>
</table>
ric closeness to each individual factor, has been completed. In addition to the orthogonal rotation method (Varimax rotation), applied have been the Quartimax rotation, Equimax rotation and Oblique rotation methods.

The tables given below illustrate the results of various variants for optimizing the factor structure at the stage of the confirmatory factor analysis. The indicated data are obtained by processing the matrix of the Spearman rank correlation coefficients. Tables 4, 6, and 8, according to the recommendations in paper [4], give values of factor loading not lower than 0.5 only.

Tables 3 and 4 show the parameters of the factor structure after using the orthogonal rotation method (Varimax rotation), with which we sought to minimize the number of variables with high loadings on each factor.

Tables 5 and 6 herein present the data obtained after applying the Quartimax rotation method, with which we tried to minimize the number of factors, required for a meaningful interpretation of each of the variables used.

Tables 7 and 8 given herein indicate the results obtained from the Equimax rotation method, which was used to simultaneously minimize the number of variables with large factor loadings and the number of factors interpreting them.

We have also completed the Oblique rotation procedure, with which we have sought to minimize the number of factors without providing their complete independence (orthogonality). It has turned out that the factor structure of the correlation relationships according to the Oblique rotation method exactly corresponds to that structure which has been obtained upon the Varimax rotation application.

As shown in Tables 3, 5 and 7, the hypothesis for an applicability of employing 4 factors for describing the optimal structure of the latent relations, provided that the analyzed objects with eigenvalues greater than 1 are referred to as the main components of the scattering ellipse axes, is confirmed for the Equimax rotation method only. Therefore, at the final stage of the confirmatory factor analysis, all the above main components calculation procedures and all the above types of their rotation have been performed for models containing only 3 factors. The results from the final stage of the confirmatory factor analysis are presented in Tables 9-14 herein.

As it is the case with all the previous stages, in order to identify the correlation relationships, we have

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<table>
<thead>
<tr>
<th>Table 2</th>
<th>Eigenvalues and percentage of an interpretable dispersion of factors after Varimax rotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor:</td>
<td>1</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Eigenvalue</td>
<td>1,02</td>
</tr>
<tr>
<td>Dispersion (%)</td>
<td>12,75</td>
</tr>
<tr>
<td>Cumulative %</td>
<td>12,75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Eigenvalues and percentage of an interpretable dispersion of factors after Varimax rotation at the stage of the confirmatory factor analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor:</td>
<td>1</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Eigenvalue</td>
<td>1,02</td>
</tr>
<tr>
<td>Dispersion (%)</td>
<td>12,75</td>
</tr>
<tr>
<td>Cumulative %</td>
<td>12,75</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Factor structure of the correlation relationships after Varimax rotation at the stage of the confirmatory factor analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ego-states</td>
<td>Number of factor</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>-0,806</td>
</tr>
<tr>
<td>2</td>
<td>-0,7626</td>
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<tr>
<td>3</td>
<td>-0,756</td>
</tr>
<tr>
<td>4</td>
<td>0,6129</td>
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<tr>
<td>5</td>
<td>0,7995</td>
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<tr>
<td>6</td>
<td>0,9271</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Eigenvalues and percentage of an interpretable dispersion of factors after Quartimax rotation at the stage of the confirmatory factor analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor:</td>
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<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Eigenvalue</td>
<td>1,85</td>
</tr>
<tr>
<td>Dispersion (%)</td>
<td>23,13</td>
</tr>
<tr>
<td>Cumulative %</td>
<td>23,13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Factor structure of the correlation relationships after Quartimax rotation at the stage of the confirmatory factor analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ego-states</td>
<td>Number of factor</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>-0,8259</td>
</tr>
<tr>
<td>2</td>
<td>-0,7874</td>
</tr>
<tr>
<td>3</td>
<td>0,6031</td>
</tr>
<tr>
<td>4</td>
<td>0,7308</td>
</tr>
<tr>
<td>5</td>
<td>0,9271</td>
</tr>
</tbody>
</table>
applied Spearman rank correlation and Kendall concordance coefficients. Since the nature of the identified relationships for each of these coefficients is the same, in our further presentation, the data for the Spearman rank correlation coefficients are given only because of greater generality of the latter. Tables 10, 12 and 14 herein show factor loading values up to 0.1 for the purpose of a more detailed analysis of the latent relations.

Table 9 and 10 given herein indicate the parameters of the factor structure after using the orthogonal rotation method (Varimax rotation).

Tables 13 and 14 herein show the results upon completion of the Equimax rotation procedure.

At the final stage of the confirmatory factor analysis, the Oblique rotation procedure has been also completed. As it is the case with the 4 factor model, the factor structure of the correlation relationships according to the Oblique rotation method exactly corresponds to that structure, which has been identified upon completion of the Varimax rotation procedure.

As shown in Tables 9, 11 and 13, the hypothesis for the applicability of using 3 factors to describe the optimal latent relations structure, when the analyzed objects with eigenvalues greater than 1 are referred to as the main components of the scattering ellipse axes, has been verified in full. The marker variables, which allow us to give a clear interpretation of their possible nature, remain the same under all types of rotation for factors similar in structure. The above marker variables are as follows:

- for factor 1: the SI values obtained when the respondents simultaneously focus on those metaphoric cards, which are associated with their highest readiness/best conditioning for their exam, examination period and successful overcoming a life's trial;
- for factor 2: the SI values obtained when the respondents focus on those metaphoric cards, which are associated with their unreadiness/worst conditioning for the exam;
- for factor 3: the SI values obtained when the respondents focus on those metaphoric cards, which are associated with their highest readiness/best conditioning for a given exam only.

Thus, the latent relations between the obtained data may be compactly described with the use of three, practically unipolar, factors. Closeness to unipolarity for each of these factors is provided by unidirectionality of variables projections on each of them, when the factor model tends to a simple structure. As known, according to the Thurstone criteria, simple structures are built in such a way that each variable has a high loading on one factor and a low one on another in parallel [4]. As a result, it significantly simplifies an interpretation of latent relations to be identified. In our case, the metaphoric cards selected by our respondents, taking into account the commonality of the cardiac responses to the related associations, may be conditionally classified into the following groups:

1) cards—indicators of their integrative emotional readiness/conditioning for successful overcoming life’s trials;

Table 7
Eigenvalues and percentage of explained dispersion of factors after Equimax rotation at the stage of the confirmatory factor analysis

<table>
<thead>
<tr>
<th>Factor:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eigenvalue</td>
<td>1,633</td>
<td>1,739</td>
<td>1,509</td>
<td>1,128</td>
</tr>
<tr>
<td>Dispersion (%)</td>
<td>20,41</td>
<td>21,73</td>
<td>18,86</td>
<td>14,1</td>
</tr>
<tr>
<td>Cumulative %</td>
<td>20,41</td>
<td>42,14</td>
<td>61</td>
<td>75,1</td>
</tr>
</tbody>
</table>

Table 8
Factor structure of the correlation relationships after Equimax rotation at the stage of the confirmatory factor analysis

<table>
<thead>
<tr>
<th>Ego-states</th>
<th>Number of factor</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>-0,7955</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
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<td>-0,7681</td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>-0,7665</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>-0,7575</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>0,616</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>0,6952</td>
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<tr>
<td>7</td>
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<td>0,7865</td>
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<td>8</td>
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<td></td>
<td></td>
<td></td>
<td>0,9692</td>
</tr>
</tbody>
</table>

Table 9
Eigenvalues and percentage of an interpretable dispersion of factors after Varimax rotation at the final stage of confirmatory factor analysis

<table>
<thead>
<tr>
<th>Factor:</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eigenvalue</td>
<td>1,914</td>
<td>1,86</td>
<td>1,563</td>
</tr>
<tr>
<td>Dispersion (%)</td>
<td>23,93</td>
<td>23,25</td>
<td>19,54</td>
</tr>
<tr>
<td>Cumulative %</td>
<td>23,93</td>
<td>47,18</td>
<td>66,72</td>
</tr>
</tbody>
</table>

Table 10
Factor structure of the correlation relationships after Varimax rotation at the final stage of confirmatory factor analysis

<table>
<thead>
<tr>
<th>Ego-states</th>
<th>Number of factor</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>-0,8036</td>
<td>-0,3285</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0,1052</td>
<td>-0,414</td>
<td>-0,7449</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>0,1763</td>
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<td>-0,1869</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>0,324</td>
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<tr>
<td>6</td>
<td></td>
<td>0,6958</td>
<td>-0,2628</td>
<td>-0,2711</td>
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</tr>
<tr>
<td>7</td>
<td></td>
<td>0,7833</td>
<td></td>
<td>-0,1926</td>
<td></td>
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<td>8</td>
<td></td>
<td>0,5494</td>
<td>-0,4525</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2) cards-indicators of their differentiated emotional unreadiness/unconditioning for successful overcoming the certain life’s trials;
3) cards-indicators of their differentiated emotional readiness/conditioning for successful overcoming the certain life’s trials.

Special attention deserves a significant contribution to the first selected factor (conventionally it may be defined as an integrative readiness/conditioning for life’s trials) among the SI values obtained when the respondents focus on those metaphoric cards, which are associated with their unreadiness/unconditioning for their examination period. The matter is that, in their post-test interviews, many respondents have mentioned their unwillingness to once again retrieve their negative states associated with this kind of the metaphoric cards. They desired to actively use in practice the revealed chance to evoke their positive emotional states with the use of the metaphoric cards. In other words, at this stage the respondents have expressed a constructive form of their supra-situational activity aimed at a positive correction of their own emotional state (the subject-genetic nature of such supra-situational activity is described in more detail in [5-7]). In these cases, the metaphoric associative cards become effective stimulation for the creation and maintenance of positive mindset to achieve a success in overcoming significant life difficulties.

As we see from the data presented, the SI values for positive emotional states form a part of Factor 1 and 3, as a rule. The exception is those SI values recorded when the respondents focus on those metaphoric cards, which are associated with their unreadiness/unconditioning for their examination period. We have described the possible cause of this exception in the preceding paragraph.

The SI values related to the negative emotional states are the major contributors to factor 2. Moreover, this regularity and this factor structure, as a whole, are retained for all the rotation variants used. This, in addition to the fact of statistically significant differences in average SI values, also demonstrates a substantial commonality of the positive emotional states, which considerably differs from that substantial commonality of those SI values, which have been recorded for the negative emotional states.

It should be noted that the most powerful factors in all variants of rotation include both the SI values for all positive emotional states, when they have been actualized individually, and those SI values, which have been reported, when our respondents have worked with the cards, which are associated with all three positive emotional states. This suggests that the factor structure confirms that at the psycho-physiological level there is a positive training effect produced by alternate actualization of positive emotional states by the respondents using the metaphoric cards selected by them.

Conclusions

The obtained evidence data allow concluding that the metaphoric associative cards can serve not only as a forecasting tool, a sort of predictors of human behavior in certain emotionally charged, stressful situations,
but also as a means for active modeling of optimal conditioning for successful overcoming of the above unfavorable situations.

The conducted studies have experimentally confirmed the validity of our hypothesis that the metaphoric associative cards, in addition to the colorful description of the phenomena, personified by the respondents, provide and mobilize the human physiological response to a specific type thereof. It has been shown that such mobilization is manifested in a certain pattern of the cardiovascular system performance.

As it is the case with the theoretical constructs investigated by us earlier in the field of transactional analysis [2, 8], the metaphoric associative cards really assist an individual to activate his/her definite, substantively different, psychophysiological status. The transitions from one ego-state to another are actually accompanied by significant changes in the human organism performance, and, first of all, in the performance of the heart. The reliable marker of such changes is the heart rate variability assessment based on the Baevsky stress index (SI) technique.

Besides, as in [1-3], we have obtained experimental confirmation of the validity of using such a complex cardiometric indicator as the Baevsky stress index (SI) to assess the effectiveness of various psycho-correction methods. But while earlier it has been applicable to the methods of psychosomatic self-regulation and transactional analysis [1-3, 8-11], now an efficient use of the Baevsky stress index has been also demonstrated in relation to the metaphoric associative cards in correction of various types of the human behavior.

Statement on ethical issues
Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest
None declared.

Author contributions
The authors read the ICMJE criteria for authorship and approved the final manuscript.

References
Assessment of system-related hemodynamics and tissue hydration in female patients with preeclampsia

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Abstract
Hypertension disorders are reported to cover up to 10% of pregnancies in the world. It is precisely the arterial hypertension that is the leading cause of developing serious complications, long-term invalidation and high maternal and infant mortality rates. In the context of the maternal mortality, preeclampsia may be attributed to 25% of all lethal outcomes. Preeclampsia occupies the second place in the maternal mortality structure. Multifetal pregnancy is a risk factor for developing of preeclampsia. The given study has been designed to obtain main data measured in pregnant patients experiencing preeclampsia. The obtained data have been compared with parameters showing changes in intra-abdominal pressure (IAP) and biochemistry data in singleton versus multifetal pregnancies. Our study has shown that arterial hypertension in multifetal pregnancies may develop due to some factors not typical of preeclampsia pathogenesis. As a result, we may assume that establishing diagnosis Preeclampsia on the basis of arterial hypertension alone may involve an inaccuracy. Therefore, in making the proper diagnostics to differentiate between preeclampsia and other causes of arterial hypertension, it is reasonable to use some additional examination techniques like an impedance measuring method. The hemodynamic data collected therewith can be effectively used in selection of the most suitable hypotensive therapy and adjustment of infusion therapy.

Keywords
Preeclampsia, Hemodynamics, Tissue hydration, Intra-abdominal hypertension, Arterial hypertension, Multifetal pregnancy

Imprint

Introduction
According to the applicable WHO statistics data referred to 2017, hypertension conditions in pregnancies occupy the second place in the maternal mortality structure that is reported in 14% of the parturient women lethal outcomes [1,11,24-25]. As to the Russian national statistics data, at least the 19% parturient cases are accompanied by arterial hypertension. So, arterial hypertension reaching the 15,7% level ranks the 4th in the framework of the maternal mortality [4]. The high likelihood of invalidation or even maternal and infant mortality requires further particular attention to be paid to studies of possible causes and approaches to treatment of arterial hypertension [12-16]. The proposed personalized approach to health care for this sort of patients will result in a reduction of the perinatal loss and an optimization of intensive unite costs.

The aim of our study has been to identify types of possible hemodynamics disorders in singleton and multifetal pregnancies complicated with arterial hypertension. Besides, it has been designed to assess changes in fluid distribution in a pregnant woman versus the respective normal value recorded in non-pregnancy, with the use of the technique of impedance measuring. Thereupon, it has been designed to reveal a relationship between the type of the hemodynamic disorders involving arterial hypertension and the respective clinical symptoms & laboratory data.

Materials and methods
Our studies have been conducted in two groups covering a total of 154 examinees, having age-, BMI-, intervention-scope- and anesthesia-technique-comparable features. All patients have been observed in the early post-surgery period in intensive care unit after the completed caesarean section procedures involving regional anesthesia techniques. In order to find the most descriptive, typical, values in our sorted sampling data set, we have utilized the median, since it has been required to minimize effects by some outliers in the sequence that skew the average of our statistics
values [6]. Both groups are homogenous by all analyzed indices that has been established with the use of the variance estimator [7]. The main test group of the patients (n=75, with an average age of 29, an average BMI = 27) has included multifetal pregnancies versus the reference group, which has covered the singleton pregnancies only (n=79, with an average age of 31.5, an average BMI = 29.5). For all the patients, their medical history records have not contained any events of arterial hypertension before their pregnancies. Under the pregnancy conditions, for the patients in both groups, AP systolic values exceeding 140 mm Hg and AP diastolic values exceeding 100 mm Hg have been reported.

According to the latest data, preeclampsia develops as a result of a placenta anomaly that leads to a release of antiangiogenic factors of the sFlt1 type and soluble endoglinins (sEng) produced in higher than normal quantities, which provoke an endothelial dysfunction. At stage two of preeclampsia developing, permeability of the vascular walls increases that initiates a vasoconstriction, an increase in the total peripheral resistance (TPR), an activation of coagulation and thrombotic microangiopathy. Further rise in the transmural pressure triggers TPR growing and aggravates the developing pathology process [5,17-20]. All the above listed factors make an effect on developing arterial hypertension, alterations in the heart performance and, in some severe cases, even polyorganic insufficiency [8]. Based on these data, we think that for the pregnant patients suffering from arterial hypertension it is reasonable to assess the volume of extracellular liquid, which is made up of the circulating blood volume (CBV), the interstitial fluid quantity and the intracellular fluid volume. An assessment of hemodynamics data, like the total peripheral resistance (TPR), the minute volume (MV) and the stroke volume (SV), is the most informative way indicating the actual condition of the vascular bed and the heart performance status. In doing so, the contractility of the heart should be estimated preferably by assessing stroke volume values (SV). This parameter shows the most sensitivity to alterations in hemodynamics, since under developing pathology process conditions, at the stage of compensation, certain mechanisms are activated to maintain the MV values within the conditionally specified normal range [9]. So, in case of a decreased stroke volume, tachycardia develops that finally contributes to the maintenance of the MV values within their normal range. An assessment of the integral tonicity coefficient (ITC) is descriptive of the actual condition of the arterial system tonus. ITC readily illustrates what shared time takes the diastolic span within the total cardiac cycle duration. An increased value of this parameter, exceeding the norm, reaching the level of 76 ± 1,6, is an indication of the centralization in the blood supply. The respiratory variation factor (RVF) responsible for stroke volume changes is a fingerprint to characterize the venous return. The RVF normal values are within the range from 1.14 to 1.24. Values exceeding the normal parameters thereof are indicators of respiration disorders, the genesis of which are attributed to pulmonary, cardiac or combined diseases.

The collected data have been automatically analyzed with the use of monitor-equipped system KMA-AR-01 DIAMANT V11.0. The respective normal value is taken to be 100%. The norms of the MV and SV parameters have been computed on the basis of the clinical data obtained with utilization of the impedance measuring technique that involves an application of the sigma interval as a limit of allowable measurements for the given device. Based on the clinical data collected, the normal value of MV is 3.1 ± 0.7 l×min-1×m-2, and the normal value of the SV parameter in females reaches 42± 8 ml×m-2. The normal value of TPR is assumed to be 1100 – 1900 din×s×cm-5. The proper normal values of the extracellular fluid volume have been derived from the formulas by Hidalgo at al. The respective extracellular blood volume = the circulating blood volume x 2.60, where 2.60 is an empirical coefficient proposed by S.Albert. The interstitial fluid volume has been taken to be equal to the difference between the total fluid volume and the extracellular fluid volume [9]. Besides, we have calculated complete sets of the following data with the above monitor-based system as listed below: a pre-ejection period (PEP), an ejection time (LVT), an isovolemic relaxation time (IVR), a filling time (FT), a diastole time (DTI), a systole time (QX), a blood volume parameter (BV) and a homeostasis load index (HL).

Preeclampsia is a severe complication in pregnancy, and it is very often is accompanied by developing polyorganic pathology. When the first symptoms of preeclampsia appear, laboratory testing is mandatorily required to deliver the biochemistry markers as follows: Alanine Aminotransferase (ALT), Aspartate aminotransferase (AST), Blood urea nitrogen (BUN),
Creatinine, Lactate dehydrogenase (LDH), free Hemoglobin and Proteinuria.

The patients from the above mentioned groups have been examined with the use of the monitor-based equipment system KM-AR-01 DIAMANT V11.0 designed for examination of the cardiac & respiratory system performance and tissue hydration. The patient’s position in the examination should be as follows: she should be in the supine position with her head supported and arms to be placed along the body. The paired electrodes are applied within the lower third volar surface areas and on the inside surface of the legs in such a manner that the current electrodes are placed distally. The current and measuring electrodes are connected to an impedance measuring instrument. Upon expiration of 10 minutes the resistance values are recorded at a low and a high frequency, respectively. Upon recording, the values required for computation of the above mentioned different fluid volumes are delivered to a PC to be processed with the specific software. The impedance measuring technique is based on the use of the impedance phenomenon. Following this way, it should be noted that an impedance of biological tissues is a complex electrical resistance of the tissues to a harmonic signal delivered thereto. Depending on the frequency of the passing electrical signal, the tissues in an organism show different permeability. With an increase in the signal frequency, the cell membrane becomes permeable, and the total resistance of all fluids grows. Our impedance-based equipment system is capable of data recording at various frequencies and analyzing the obtained measuring results. The developed mathematical model takes into account BMI and the general state of the organism that provides for an unbiased assessment of the studied parameters in critical state patients.

Results and discussion

We have completed our studies on central hemodynamics in patients of both groups in the early post-surgery period against developing AH. According to Clinical Guidelines “Hypertension Disorders in Pregnancy and Post-Partum Period. Preeclampsia, Eclampsia. Clinical Recommendations. Treatment procedure records” approved by the Russian National Association of Anesthesiologists and Resuscitators, an abnormal increase in the AP level has been treated as a preeclampsia marker; in connection therewith the patients have received magnesium therapy in accordance with the schedule as follows: intravenous 25% magnesium MgSO4, 4000 mg within 15 minutes, subsequently micro-jet injection of 1000 mg/hr [10].

The data on hemodynamics, reported upon the studies, have shown significant differences in some indicator values. To illustrate this statement, it should be noticed that the MV and SV values: MV = 2.46 l/min·m², SV = 33.95 ml/m² recorded in the main test group have markedly exceeded those reported for the reference group: MV = 1.7 l/min·m², SV = 24.55 ml/m² (by 44% in case with MV and by 38% in case with SV, respectively). In its turn, the TPR, CBV values and extracellular fluid parameter recorded in the main test group have been found to be lower than those reported in the reference group (TPR is lower by 55%, CVB is lower by 8.5%, and the intracellular fluid volume has a decrease by 10.5%). The ITC parameter is at the lower limit of the norm (74.6) in the main test group that points to the fact that there is no peripheral vascular spasm available. The RVF parameter in the reference group patients exceeds the normal values (1,3) that bears witness to the fact that there is a strong impact of the intrathoracic pressure on the venous return. A brief survey of the compared hemodynamics data are given further herein in Table 1.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>APs / APd, mmHg</th>
<th>MV, l/min·m²</th>
<th>SV, ml/m²</th>
<th>TPR, mmHg·sec·cm⁻²</th>
<th>ITC</th>
<th>RVF</th>
<th>PEP, sec</th>
<th>LVOT, sec</th>
<th>IVR, sec</th>
<th>FT, sec</th>
<th>DTI, sec</th>
<th>QX, sec</th>
<th>HL</th>
<th>BV, %</th>
<th>Extrac.Fl, %</th>
<th>Intrac.Fl, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main test group</td>
<td>163 / 95</td>
<td>2.46</td>
<td>33.95</td>
<td>1936</td>
<td>74.6</td>
<td>1.23</td>
<td>0.12</td>
<td>0.32</td>
<td>0.17</td>
<td>0.26</td>
<td>0.44</td>
<td>0.44</td>
<td>114</td>
<td>107</td>
<td>105</td>
<td>98</td>
</tr>
<tr>
<td>Reference group</td>
<td>165 / 107</td>
<td>1.7</td>
<td>24.55</td>
<td>3014</td>
<td>75.9</td>
<td>1.3</td>
<td>0.12</td>
<td>0.3</td>
<td>0.15</td>
<td>0.27</td>
<td>0.43</td>
<td>0.42</td>
<td>100</td>
<td>116</td>
<td>115.5</td>
<td>99</td>
</tr>
</tbody>
</table>
The recorded significant differences in the lab biochemistry data have engaged our attention, too. The deviations of the most important markers of preeclampsia ALT, ACT and LDH have been reported to be doubled values in the reference group, and the respective values of biochemistry in the main test group have primarily remained within the tolerable range. The proteinurea level in the main test group has reached 0.8 g/l, and the averaged level thereof in the reference group has been reported to be 4.5 g/l that is an indication of involvement of kidneys in pathology process. Intra-abdominal hypertension in the reference group is added to the developing preeclampsia process as mentioned above. In the main test group, the average IAP value has remained at the upper limit of the norm. The major biochemistry markers of preeclampsia are summarized by Table 2 given further herein.

The validity of the survey statistics data on the main test group patients shows that the arterial hypertension pathogenesis in multifetal pregnancies may be related to the stroke volume parameters. As to the reference group, covering the singleton pregnant patients, high TPR levels, indicating vascular spasm, may be treated as the deciding factor for developing AH. The increased averaged values of the extracellular fluid volume, exceeding the norm by 15.5%, in the reference group patients with singleton pregnancies demonstrate that there is an increase in the interstitial fluid volume that may partly explain the high averaged BMI valves of the mentioned patients that is manifested by pronounced edema cases.

Table 2

<table>
<thead>
<tr>
<th>No. of ind.</th>
<th>BMI</th>
<th>Age, years</th>
<th>Hb, g/l</th>
<th>Ht, %</th>
<th>PLT, 10⁹/l</th>
<th>Urea mmol/l</th>
<th>Phosphocr, µmol/l</th>
<th>ALT, Un./l</th>
<th>AST, Un./l</th>
<th>Free Hb, g/l</th>
<th>LDH, Unl</th>
<th>Proteinur., g/l</th>
<th>IAP, cmH2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main test group</td>
<td>75</td>
<td>27</td>
<td>29</td>
<td>110</td>
<td>32</td>
<td>184</td>
<td>4</td>
<td>68</td>
<td>32</td>
<td>36</td>
<td>0.22</td>
<td>375</td>
<td>0.8</td>
</tr>
<tr>
<td>Reference group</td>
<td>79</td>
<td>30</td>
<td>31.5</td>
<td>111</td>
<td>34</td>
<td>177</td>
<td>4.7</td>
<td>75</td>
<td>63</td>
<td>77</td>
<td>0.66</td>
<td>628</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Conclusions
1. With respect to developing AH in the main test group covering multifetal pregnancies, attention should be drawn to the fact that there is a relatively high level of the SV (MV) parameter with the normal TPR data. The obtained evidence data show that AH in multifetal pregnancies may develop without vascular spasm.
2. The conducted studies have demonstrated that Arterial Hypertension in the singleton pregnant patients from the reference group develops fully in accordance with the modern concept of the preeclampsia pathogenesis.
3. Administration of the proper hypotensive therapy, considering the pathogenesis aspects in a proper manner, taking into account the systemic hemodynamics data and tissue hydration assessments, can produce a positive outcome in the therapy with minimized medication.
4. The corrective measures to improve the infusion loading on the basis of the tissue hydration assessments are substantiated by the valid pathogenesis assumption.

Statement on ethical issues
Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest
None declared.

Author contributions
The authors read the ICMJE criteria for authorship and approved the final manuscript.

References
Signal morphological criteria for cardiotoxicity in breast cancer chemotherapy

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Aims
A high incidence of breast cancer is observed in all countries throughout the world, and this dictates the use of aggressive antitumor drugs. The toxogenic effect of anthracycline drugs on the cardiovascular system under conditions of oncological pathology determines the need to expand the diagnostic capabilities for detecting cardiotoxicity, including searching for signal morphological markers in blood serum. The aim of this work is to study the structure of solid-state films of blood serum in patients with breast cancer at the stages of their chemotherapeutic treatment to identify signal criteria for cardiotoxicity.

Materials and methods
Studies were conducted in 25 patients with primary breast cancer (BC) with an extent of spread of the tumor process corresponding to T2-4N0-1M0. Polychemotherapy (PCT) was carried out in a neoadjuvant regimen, which included doxorubicin (60 mg/m2) and cyclophosphamide (600 mg/m2) supported by echocardiography examinations and ECG monitoring. Morphological testing of solid-state blood serum samples was carried out using the Shatokhina-Shabalin method of wedge-shaped dehydration both before PCT and in the course thereof. Samples were visualized with the Leica DMLS2 microscope with a magnification from x20 to x90.

Results
Before starting the PCT course, in the serum facias, in 55% of the cases detected has been the loss of the radial symmetry system and the formation of pathological types, including the “double” facias that is a criterion of systemic intoxication. Local markers of comorbid states with a detection rate of up to 40% of intoxication, impaired vascular elasticity, sclerosis, hypertension and ischemia have been identified. After 3 courses of PCT including anthracyclines, the occurrence rate of formation of these pathological criteria increased by 1.7 times; the occurrence rate of myocardial trophic disorder markers was found to be higher. At stages 5–6 of the treatment course, in 80% of the cases, some signal signs of the cumulative effect of anthracyclines associated with impaired cardiac rhythmogenesis were detected in the facias structure.

Conclusions
Inhibition of tumor growth under PCT including anthracyclines is accompanied by structural deformation of the systemic and local self-organization of blood serum. An intensification of crystallization of inflammation pathological proteins, sclerosis, intoxication, hypertension, stagnation angiospasm and cardiac arrhythmias makes it possible to assess the intensity of drug cardiotoxicity using the identifying markers, predict long-term effects of PCT and a possibility of their prevention.

Keywords
Breast cancer, Anthracycline, Cardiotoxicity, Blood serum morphology

Imprint

Introduction
A significant occurrence rate of breast cancer (BC) and a high mortality rate in females make the issues of the BC treatment and diagnostics of patients topical [1]. Chemotherapy is known to be one of the leading methods of treating breast cancer, and the most effective drugs for the therapy are anthracyclines, taxanes, alkylating agents, fluoropyrimidines and trastuzumab [2]. With extending growth of medication options, the risk of cardiovascular complications also increases. Antitumor agents of various classes may produce a pathogenic effect on the cardiac muscle and contribute to the development of functional disorders, including cardiac arrhythmias, myocarditis, pericarditis, infarction, acute or congestive heart fail-
ure. Within the range of various complications of the anthracycline antitumor therapy, cardiotoxicity is of particular danger [3, 4]. This spectrum of events may occur either immediately or years upon the CT completion, therefore, it is so important to identify eligible operational prognostic criteria for cardiotoxicity, indicating the need for correction of cardiovascular pathology [5, 6, 7].

The appearance of functional and structural changes in the heart and blood vessels is reflected in the circulating blood composition. It is known that blood transports toxic substances (tissue destruction products, incomplete protein-, lipid- and mineral exchange-related metabolism products), therefore, the presence of toxins in blood, i.e. toxemia, is a pathological state that can be detected in blood testing. Along with the earliest biochemical criteria for intoxication, there is an important condition that indicates that the non-cellular component of blood (plasma, blood serum), in addition to the detectable biochemical (dynamic) changes, can serve as an important source of information about the formative (static) characteristics of the fluid phase, when the blood fluid is transformed into its solid state. This unique approach to the diagnostics of pathological states was developed by Russian scientists, Member of the Russian Academy of Sciences (RAS) Shabalin V.N. and Corresponding Member of RAS Shatokhina S.N. They created the methodological basis for biological fluid morphology [9-10]. The methods proposed by the above researchers for the diagnostics of the morphological structure of blood serum and other biological fluids are supported by the description of the criteria for identifying pathological states and their structural features, which have found applications in assessing effects made by different therapeutic factors [10-13].

The aim of this research work is to study the structure of solid-state films of blood serum in patients with breast cancer (BC) at the stages of their chemotherapeutic treatment for identifying signal criteria for cardiotoxicity and determining their prognostic value.

Materials and methods

The study included 25 patients aged under 50 (49.8 ± 0.5) with primary breast cancer (PBC). The extent of spread of the tumor process has been found in 90.5% of patients to correspond to T2-4N0-1M0. Polychemotherapy (PCT) was carried out in a neoadjuvant regi-

men with doxorubicin (60 mg / m2) and cyclophosphamide (600 mg / m2) included. Before the fourth course of PCT and upon completion thereof, a control assessment of the cardiovascular system functional state was carried out using standard echocardiography and ECG examinations. In doing so, the following concomitant diseases were diagnosed: arterial hypertension, chronic heart failure (71.4%), myocardidystrophy (12%), and, in some individual cases, heart rhythm disturbance, diabetes mellitus, autoimmune thyroiditis and hyperalimentation. According to the indications, omeprazole, prednisolone, ademetionine, inosine and famotidine were prescribed as accompanying therapy. All research protocols were prepared in accordance with the ethical standards according to Declaration of Helsinki (1964) and approved by the Ethics Committee at the Federal State Budget Scientific Institution RRIO, Ministry of Health, Russia. The structural markers of cardiotoxicity were detected using the method of wedge-shaped dehydration developed by Shatokhina-Shabalin. To obtain solid-state blood serum samples, venous blood was collected with a sample volume of 2 cm3; cell elements were separated by centrifugation, and the resulting biofluid was applied dropwise onto a glass slide with a volume of 10 μl. The duration of the dehydration process was 18–22 hours; it was conducted at a temperature of 22–24° C with a humidity of 65–70% under open air conditions without direct air flows. The morphostructure of the solid-state film of serum was evaluated using light, dark and polarization microscopy with the Leica DMLS2 microscope with a magnification factor from x20 to x90. The terms and definitions related to the morphological structures of blood serum and the markers of pathological processes have been applied in accordance with the original reference source by V.N.Shabalin and S.N.Shatokhina.

Results

The study of morphology of the solid-state blood serum samples in the BC patients before PCT including anthracyclines revealed initial disorders in the systemic self-organization thereof. This was evidenced by the absence of the full radial symmetry of the cracks, the appearance of zigzag-pattern beads and ridges along the circumference line in the boundary and intermediate zones of the facias. In 45% of the cases a partially radial morphotype of the facia has been detected, in 35% of the cases an irradial morphotype...
thereof has been identified, and in 20% of the tests the formation of an extremely unfavorable morphotype, the so-called “double” facia has been discovered that marks a highly toxic state of biofluid (see Figure 1 herein).

The pronounced invariance of the pathological serum morphotypes before PCT indicated the influence of the malignant process on the organism and made it possible to identify paraspecific signs of the tumor growth (see Figure 2 herein). The paraspecific signs primarily included such structures as “wrinkling” and “toxic plaques”, representing markers of intoxication and toxin products of the liquid medium, which were detected with an occurrence rate up to 35-40%. Before the treatment, in a quarter of the examined patients with initial cardiac arrhythmias, a signal marker of extrasystole, a “finger-shaped structure”, was found. In 25% of the cases, markers of chronic inflammatory processes were recorded, which were shaped like regional fields of some crystallized inflammatory proteins building structures of the split Arnold tongue type and the Sierpinski carpet type. The occurrence rate of impaired vascular elasticity markers, namely, the structures like "silver cracks", as well as sclerotic processes in blood vessels, i.e. the “leaf”-type structure, increased to a level of 40%.

Thus, the initial picture of the solid-state blood serum samples in the above mentioned cohort of the BC patients indicated that, against the background of systemic disorders in the self-organization in biological fluid, the revealed paraspecific signs did not differ from those revealed with the conventional equipment and instrumentation used for diagnostics of cardiac and vascular pathology in the patients before their drug treatment. It is no doubt that the tumor itself makes a vast contribution to the development of the above disorders under the localized malignant process conditions. Of considerable interest was our analysis of the initial morphotypes with samples obtained after the first three courses of PCT, which limited the pathogenic effect produced by the tumor, but provoked at the same time the side effect of enriching the internal environment with aggressive drugs and their metabolites.

The completion of 3 courses of antitumor PCT with anthracyclines included significantly affected the structure of the serum facias. First, the partially radial morphotype of the facias, which is closest to the normotype of the radial symmetry, was completely lost. The pathologically stable morphotypes, namely the ir-radial and the circular types with a pronounced asymmetry and a chaotic distribution of cracks, which indicated a systemic disorganization of the facia structure, were dominant. Second, some morphological signs of chronic insufficiency of cerebral and cardiac circulation of the hypertonic and atherosclerotic genesis were revealed in the form of a circular arrangement of band-type cracks against the background of the three-ray ones (see Figure 3 herein). The above suggestion was confirmed by the presence of structures like "silver cracks", which made us possible to identify disorders in the blood vessel elasticity and hypertension. The most frequently found marker of hypertension and angiospasm was a cluster of the “scallop struc-
Figure 2. Fragments of serum facias in BC patients before PCT: a) a cluster of pathological markers of intoxication and inflammation: "wrinkling" of toxic proteins in the boundary zone and signs of the Arnold tongue types in the intermediate zone; b) a cluster of markers of inflammation: markers of the Arnold tongue types, markers of angiospasm and hypertension: "scallop" structures; c) sclerosing markers: the "leaf" structure visible using the polarized light; d) "scallop" structures and "silver cracks". Magn.x 20, x 40.

Structures” in the boundary zone of the facias, at the base of which there were lines of dash-type cracks. During the systematic use of hypotensive drugs by BC patients, the structure of “the scallops” was transformed into broken lines, and the presence of “the dash-type cracks” demonstrated the possibility of a compensatory development of the microcirculatory network to restore the blood supply in those areas of the brain or the heart tissues affected by hypoxia or ischemia, that was observed in 50% of the cases.

In addition, in 60% of the cases, detected were the markers, which manifested a myocardial trophism disorder and which contained the "spike" type structures of various sizes in large and small cracks of the facias. At the considered stage of the treatment, an increase in the occurrence rate and enlargement of local structures of the “toxic plaques” and “wrinkling” structures built by toxic proteins, toxins and incomplete metabolism products, was observed, that determined a high level of general intoxication and was directly related to cardiotoxicity.

At the subsequent stages of the treatment, especially by the time of the completion of courses 5-6 of antitumor PCT in the BC patients, the further cumulative effect produced by anthracyclines had negative consequences associated with cardiac arrhythmias. In parallel with the clinical recording of these abnormalities, in solid samples of patients’ blood serum, specific inclusions typical to atrial fibrillation were revealed. The inclusions represented small dual structures of triangles located within the doubled Arnold tongue type regions and the Sierpinski carpets (see Figure 4 herein).

It should be noted that before PCT including anthracyclines this sort of structural markers was not detected. A significant increase in the occurrence rate of the "spikes" structure (up to 80% of the cases) at large cracks also confirmed the presence of disorder-
Figure 3. Fragments of serum facias in BC patients upon completion of the 3rd course of PCT with anthracyclines included: markers of chronic insufficiency of peripheral (a) and central (b) blood circulation: the circular arrangement of band-type cracks; c) markers of myocardial trophic disturbance: "spikes" structure; d) fractures and alignments of the "scallop" structures as markers of angiospasm and hypertension in accompanying therapy. Magn. X 40.

Conclusions

As evident from the completed monitoring of the blood serum facias in the BC patients at the stages of antitumor PCT including anthracycline drugs, the processes of structural self-organization of the biofluid undergo pronounced transformations both at the systemic and local levels. Prior to starting the drug therapy, detected were clear morphological signs of the pathogenic effect produced by a malignant tumor on the organism, reflecting the loss of normotypes of the radial symmetry and the formation of the “double” facia, the marker of intoxication. At the same time, the processes of the cancer-related intoxication were complicated by comorbid conditions, which manifested themselves at the level of local crystallogenesis of pathological proteins of inflammation, sclerosis due to intoxication, hypertension, angiospasm of congestive events, cardiac arrhythmias in the form of identifying paraspecific markers. Thus, before the treatment, the level of the damaging effect produced by the tumor on the internal environment state was adequately assessed.

As the tumor growth was inhibited, the markers did not disappear: on the contrary, they became a reflection of the side effects made by doxorubicin and cyclophosphamide. Our study of the facias, especially at the final stages of PCT, has demonstrated cumulative effects, which aggravate the systemic self-organi-
Figure 4. Fragments of serum facias in BC patients upon the completion of 5–6 courses of PCT with anthracyclines included: a, b) markers of atrial fibrillation: the structures of triangles in the double Arnold tongue regions c) the "spikes" structure at large cracks of the facias in case of heart rhythm disorders; d, e, f) markers of extrasystole: the "finger-shaped" structures. Magn. x 40, x 90.
zation of the facias and add to the complexity of the cardiopathology up to the appearance of atrial fibrillation markers. An increase in the occurrence rate of detecting the “finger-shaped” structure markers, linked with an increase in the Sierpinski carpet areas and the Arnold tongue type regions, associated with their texture of multiple triangles, which are possibly associated with degenerative changes in cardiomyocytes, may bear witness to a progression of the myocardial strain tension related to the rhythm-generating system. As shown by Shatokhina S.N. and Shabalin V.N., abnormal structures of the solid-state phase of blood serum are formed by pathological metabolites and can be found in a variety of their combinations with other structures. In other words, cardiotoxicity is targeted not only at the muscle system, but also at the nervous system of the heart, represented by structural elements highly sensitive to toxins.

It should be pointed out that medical monitoring of the cardiovascular system state and mandatory accompanying therapy for patients during the entire period of their treatment certainly produced a cardiotropic effect that made it possible to suppress the toxic attack of anthracyclines and provide the required completion of the PCT courses. At the same time, the possibility of additional testing and identification of the anthracyclines’ toxic effect markers may have a great prognostic value considering a reduction in the risk of delayed adverse effects made by anthracyclines, well-timed administration and completion of the required supportive cardiotropic therapy.

Statement on ethical issues
Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest
None declared.

Author contributions
The authors read the ICMJE criteria for authorship and approved the final manuscript.

References
The study of hemodynamics in critical patients under intensive care unit conditions

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Introduction
Studies of hemodynamics in critical patients under intensive care unit conditions have been a very difficult task until now [1]. There are a number of reasons for that. No instruments capable of noninvasively recording data on hemodynamics and metabolism, as well as the cardiovascular system performance, could be used. Of course it is reasonable that, according to the relevant methodology, all the data should be recorded on the ‘here-and-now’ basis, in real time, to enable rapid decision-making in order to save the patient’s life. Such possibilities have not been available. Only heart rate and blood circulation were monitored, i.e. the parameters that can be informatively evaluated post factum only and that cannot be used to predict the organism state. This paper presents results of noninvasive examinations in critical patients in an intensive care unit with the use of the cardiometric method. The method is implemented using device Cardiocode designed and manufactured for cardiology diagnostics [2]. Using the device it becomes possible to estimate the boundaries of critical states, which allows predicting the development of the patient’s condition and make adequate decisions without any delay at the bedside.

Aims
The aim of the study is to analyze the hemodynamics data recorded in critical patients under the intensive care unit conditions.

Methods
The methods thereof is based on the ECG recording, identification of the cardiac cycle phases and the automatic mathematical calculation of the following parameters:

1. Hemodynamic parameters
   - SV - stroke volume of blood, ml;
   - MV - minute volume, l/min;
   - PV1 - volume of blood entering the ventricle during early diastole phase, ml;
   - PV2 - volume of blood entering the left ventricle during atrial systole, ml;
   - PV3 - volume of blood ejected by the ventricle during rapid ejection phase, ml;
   - PV4 - volume of blood ejected by the ventricle during slow ejection phase, ml;

   *Submitted: 2.02.2020; Accepted: 18.03.2020; Published online: 21.05.2020*
PV5 - blood volume (part of SV), pumped by the ascending aorta as a peristaltic pump, ml.
RV1 - ejection fraction, %.

2. Parameters of metabolism
Qualitative assessment of metabolism in the cardiac muscle fiber cells:
- Aerobic biochemical reaction (oxygen level) (in arbitrary units);
- Glycolytic reactions (lactate level) (in arbitrary units);
- Level of phosphocreatine (in arbitrary units).

The experimental studies have been conducted with the use of hemodynamic PC-assisted analyzer "Cardiocode", Approval No. RU 26797 issued by Roszdravnadzor, July, 12, 2011, Specifications TU 9441-001-73270813-2006.

The research study program has included the following:
1. Noninvasive hemodynamic examinations at least in 30 patients under critical conditions in intensive care unit.
2. Studying diagnosis of each examinee’s according to his/her medical history at admission to hospital.
3. Recording the cardiometric parameters on the basis of periodic monitoring.
4. Identifying the boundaries in the critical hemodynamic and metabolic parameters, beyond which the lethal outcome occurs.

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Figure 1. Cardiometric data upon completion of one measurement procedure.

Figure 2. The monitoring data on hemodynamics in the above patient. Six measurements have been made.
Results and discussion

The cohort of 36 patients has been covered by the above hemodynamic examinations, and 28 of the examined patients have died. The obtained information was compared with the medical history records issued to the patients before admission to hospital. Findings prepared by pathologists have been also obtained and considered herein. Some summarized data on the patients are presented in a table given further herein.

Figures 1 and 2 herein show cardiometric data in one of the critical patients treated in an intensive care unit. After careful examination of the screenshots you can see that the PV1 and PV2 phase blood volumes have changed. As to parameter PV1-atrial systole, it has been reduced: its deviation from the norm reaches 36.17%, while the ventricles are overloaded by 23.50%. The PV5 parameter representing the aorta pump function is also overloaded by 5.36%. The oxygen concentration is 0.29 arb.u., and it is significantly below the norm. It is evident that the heart accumulates lactate. While the normal value of lactate is 7 arb.u., in our treated case we record the actual lactate level of 26.39 arb.u.. The phosphocreatine concentration is also below the norm and reaches 0.17 arb.u.. But it is important that the RV1parameter of ejection fraction is 15.31% that is very low as compared with its norm of 62%. The respective Rheo shows blood pressure spikes that confirms weakness of the heart performance.

Figure 2 herein shows the monitoring results in the same critical patient: next six measurements have been made. The resulting diagrams show that in parallel oxygen, lactate and phosphocreatine concentrations have decreased below the norm in the patients before his lethal outcome. The ejection fraction parameters in this case have been also decreased dramatically. At the same time, the stress index SI values demonstrates its sharp increase. Next day the patient died.

Other phenomena, which have occurred before the death, have been also recorded. The most pronounce regularity has been detected in our analysis of the recorded heart rate variability values. So, before the death stress index SI has increased sharply and exceeded the level of 1000 (see Figure 2 herein) that indicates the presence of one and the same heart rate level. Immediately prior to the lethal outcome, the variability has been restored.

The phenomenon of the restoration before the lethal outcome has been observed in all segments of the ECG complex. It has seemed that the critical patient suddenly have become fully healthy. AP has been maintained at the same level.

One more factor of interest is the S-L phase elevation. This is a compensatory mechanism for maintaining the proper hemodynamic parameters, and the elevation appears under critical conditions. In our case it has been reported before each fatal outcome. An ECG with the S-L phase smoothing has been also recorded. It refers to the case of "the adrenaline heart", when Ca++ accumulates in large quantities in cells and disrupts mitochondrial membranes that leads to a decline in the myocardial contraction. It also has led to the patients’ death.

Before the death, the rheogram curve rises with each inhaling and falls with each exhaling; if the respiration rate is low, the critical patient can live up to 12 hours. The performance of the lungs makes a direct effect on the rheogram shape, since the lungs are capable of supplying blood before the critical patient's unfavorable outcome. In case when the Cheyne–Stokes respiration is found, then after 12 hours, such a critical patient dies.

Conclusions

The obtained evidence data have been properly analyzed, so that identified are those critical values of the hemodynamic and metabolic parameters, the exceeding of which leads to lethal outcome in critical patients under the intensive care unit conditions.

1. Diagnostic efficacy of the identified criteria applicable to critical hemodynamic and metabolic parameters in intensive care unit patients, exceeding of which leads to lethal outcome, is high and sufficient to provide effectively decision-making.
2. Prior to the lethal outcome, there is a rise in the stress index value observed: it demonstrates a sharp increase over 1000.
3. In the period immediately before the lethal outcome, themodynamics is provided due to the lungs performance.
4. Simplicity and accessibility of the diagnostic method is based on using an electrocardiogram processing only.
5. The data of high value are obtained very easy and fast due to automatic data processing technology.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.
Conflict of interest
None declared.

Author contributions
The authors read the ICMJE criteria for authorship and approved the final manuscript.

References
Evaluation of general repolarization of cardiomyocytes with biphasic pulses of different shapes

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Abstract
According to data provided by the European Resuscitation Council (ERC), 76% of sudden cardiac arrests should be attributed to ventricular fibrillation [1-3]. The main treatment of this disease is an immediate cardiopulmonary resuscitation, one of the components of which is a defibrillation of abnormal rhythms. The paper presents an analysis of advanced shapes of biphasic pulses, which have found a widespread application and have been clinically tested. The aim is to study the main parameters of the impact of different shapes of the existing pulses and their due consideration in a development of a defibrillator. An evaluation has been performed using defibrillators Fluke Impulse 7000DP and device Impulse 7010 designed to simulate different loads. Evaluated has been the shape of each of 7 biphasic pulses, the amplitude and exposure time of each of different signal phases. Upon results of the conducted analysis, some recommendations on cardiopulmonary resuscitation have been prepared; in particular, the necessity to maintain a constant current density of 14 -16 A, delivered for 4 -5 ms, is proposed. The maintenance of these parameters can be provided using the current stabilization technology (CST).

Keywords
Biphasic pulse, Defibrillation, Cardiomyocytes repolarization, Ventricular fibrillation, Current-controlled defibrillation

Imprint

Introduction
Sudden cardiac arrest (SCA) is one of the leading causes of death in developed countries. According to data provided by the European Resuscitation Council (ERC), in 2015, 76% of sudden cardiac arrests should be attributed to ventricular fibrillation (VF) [1-3]. A marked increase in the VF share has been identified after taking active measures to apply automated external defibrillators (AED) [4-5] available at all the important public places. The main treatment of SCA is an immediate cardiopulmonary resuscitation (CPR) and defibrillation of abnormal rhythms, such as VF and ventricular tachycardia (VT). The AED availability and an early, within 3-5 minutes, defibrillation can raise a survival rate up to 50-70% [3,5,6].

The basic characteristics of defibrillators operating in manual and automated modes are the range of energies that the defibrillator is capable to produce, their pulse shape and their charging/discharging time. The first discharge shock energy for adults is 150 J with a possible further increase in case of inefficacy [7-9]. For adolescents aged 1 to 8 years in case of using manual defibrillators, it is necessary to use energy from 4 to 9 J / kg in the range of 50 -75 J [10-13]. As to the shape of the pulse used, they are biphasic in all modern defibrillators. A higher efficiency of the bipolar pulse in comparison to the monopolar one is supported by a large number both of theoretical and practical works [14-16]. The basic concept of the time requirement is to minimize it from the beginning of the rhythm detection to the readiness to discharge. Based on the duration of the proper defibrillation it is found that the time and amplitude of the second pulse phase should be lower. This parameter varies from one manufacturer to another, and each of them submits its own justifications of why to produce its own type of circuitry.

The pulse energy, its shape and the time should be optimal and serve two purposes. The first purpose is to provide a complete and simultaneous repolarization of all cardiomyocytes, and the second one is to reduce damaging negative effects made on cardiomyocytes. The major damage is done to mitochondria of cardiomyocytes, cristae of which are destroyed due to
the action of high level energy. According to studies conducted in mice, the restoration of the above damaged structures takes longer than a week and may be irreparable [17]. The above mentioned purposes can be achieved using the current stabilization technology (CST), which provides constant current strength throughout the entire discharge, that makes the pulse almost rectangular and eliminates peak current fluctuations damaging the myocardium, which are typical to other pulse shapes (exponential, trapezoidal, sinusoidal type, etc.). Based on the above, a development of a defibrillator requires a careful analysis of electropulse therapy (EPT) technologies and mathematical modeling of an impact produced by shapes of defibrillating.

The aim herein is to analyze and develop the optimal shape of an acting pulse for an external defibrillator.

Materials and methods

We have studied different pulse shapes, which have been clinically tested and used in automated and manual defibrillators. Our analysis is based on the impact of a biphasic pulse on cardiomyocytes. The following main energy characteristics of the defibrillator are compared: the shape, the duration and the amplitude of a pulse, as well as dependencies of these parameters on the load resistance magnitude, charging voltage and capacitance characteristics of a capacitor.

The study has been conducted with the Fluke Im pulse 7000DP analyzer of defibrillators in transdermal pacemaker, with the use of an additional device Im pulse 7010 for the selection of a defibrillator load.

Results and discussion

7 different types of pulses used in defibrillators for electropulse therapy have been investigated. Results of our studies are given below.

"The smart biphasic pulse" widely used in electropulse therapy practice is based on the 95 μF capacitor, which is charged up to 1625 V (energy 115 J) or 1800 V (energy 130 J), employing the 120 μF capacitor with a charge of 1800 V at a nominal pulse having an energy of 180 J.

At the onset of each pulse, a chest impedance has been assessed with serially connected resistors having a resistance of 22 ohms for 50 μs. During this period of time the patient’s impedance is determined, which should be at least 22 ohms. Based on the measured impedance, the time is specified in such a way that the nominal energy would be delivered in full. During our studies the pulses with an energy of 200 J and an impedance of 25, 50, 100 and 125 ohms have been applied. The measurement results are shown in Figure 1 herein.

Figure 1 shows that the pulse duration and its amplitude are highly dependent on the chest impedance. The ratio between the first and second phase current strengths is relatively constant in the pulse [18].

As opposed to the smart biphasic system, the "adaptive biphasic pulse" protocol is implemented with a possibility to adjust the delivered energy up to 360 J. To deliver this energy, in the circuit used is a capacitor of 210 μF that makes the pulse more prolonged. The results of measuring the pulses with an energy of 200 J at an impedance of 25, 50, 100 and 125 ohms are shown in Figure 2 herein.

As seen from the diagram in Figure 2, the feature of an adaptive pulse is a constant ratio between the second phase and the first one, which is always 2/3 of the first phase, regardless of the impedance. This compensates for internal losses, especially in patients with a low resistance, and slightly shortens the pulse duration in patients with a high resistance, so that with these changes make possible to maintain the rated output power always at the same level.

A self-compensating output signal of envelope-type pulse SCOPE (Self-Compensating Output Pulse Envelope Waveform) is widely used in the EPT practice. The feature of the circuitry of the defibrillators employing this type of pulses is the following sequence: capacitor - resistor - patient. It is just in this area where an evaluation of the patient impedance occurs. The pulse is provided with a capacitor of 120 μF. According to the studies conducted by the pulse technique developers, even in patients with a high resistance (> 100 ohms), the defibrillation is carried out successfully with a pulse energy of 100 J. A protocol of use of the defibrillators with this signal type has been adapted to circuit 150 J - 150 J - 200 J according to ERC2015. The diagram of studies on SCOPE pulses with an energy of 200 J at a load of 25, 50 and 100 ohms is shown in Figure 3 herein.

The diagrams show that both phases always have the same duration. In general, this sort of pulses is very similar to the "smart pulse", which shortens the second phase in case of longer pulses.

"Orbital biphasic pulses" illustrated by Figure 4 herein are positioned as low voltage (maximum voltage of 1350 V) defibrillation pulses. They are provided by capacitors of a high capacity of 500 μF.
Figure 1 shows that the signals are characterized by a prolonged pulse duration (up to 35 ms with a high resistance). Previously it was assumed that it was impossible to efficiently use the technology in patients having a high resistance. However, some studies in animals have demonstrated the opposite. Studied were 6 dogs weighing 21.6 to 34.5 kg, and it was found that the defibrillation threshold was from 20 to 30 J, which was comparable with the biphasic defibrillator with a voltage of 2 kV. Patients with a high resistance were modeled with an additional resistor of 32 ohms, the threshold defibrillation rose to 34.3 J. Despite the obtained results, which are not typical to humans, developers believe that the orbital biphasic pulses may be applicable to humans.

Figure 5 gives a "multipulse" discharge type, which demonstrates a feature to represent each phase in the form of pulses with a frequency of 5 kHz and a pulse/pause ratio of 1:1. Finally, the single-phase pulse studies have shown that such pulses behave as a closed signal of a medium current strength [19,20]. As is known, the pulse energy depends on the square of the current, and a pulse interruption leads to an increase in energy requirements. This is compensated by the fact that the declared pulse duration is closer to the minimum necessary for the cardiomyocytes excitation, in comparison with the biphasic pulse shapes as discussed above.

Figure 5 gives an illustration of fundamental differences between the "multipulse" discharge from the previously described discharge techniques, but in fact this is a standard bipolar exponentially truncated signal. The protocol of the energy increase recommended by the developers implies starting with 90 J and maximizing up to 180 J. The energy of 180 J is positioned as a "threefold energy margin".

Used is the so-called STAR discharge which represents a biphasic pulse. It has long been considered to be optimal from the standpoint of the structure of the second phase, which consequently implements the theory of "a charge balance". The patents describe a debatable discrete equivalent circuit diagram and some findings associated therewith [21,22]. Impedance is mentioned as an additional feature, although its importance cannot be underestimated [23]. These facts do not allow us considering the "STAR pulse" as a relevant pulse circuitry.

As a "linear" pulse described is a pulse, which in the first phase is close to a rectangular pulse with a constant current of 15A. It is emphasized that the time is constant for any allowable resistance. This is sup-
ported by the results of the pulse test, presented in Figure 6 herein.

Thanks to the constant current density the efficacy considerably increases, especially in the patients with a low resistance. The patients with a high resistance, in their turn, are exposed to a standard bipolar pulse, which is relatively shorter than the above one. From the standpoint of engineering, the pulse shaping is provided with the use of serially connected resistors, the required set of which is switched depending on the patient’s actual impedance [24]. An imperfection of this circuit is a high voltage, when discharging to low resistance, despite the stated CCT system.

The "biphasic" pulse peculiarity is a programmable switch, which allows changing the ratios of the delivered energy. In the design settings, the developers preset the ratio of energies as 90% in the first and the remaining 10% in the second phase. When testing the signal, the first pulse duration always is 4 ms, which is the optimal time to complete repolarization according to numerous studies [15]. As it is the case with the previous signal, this can be realized at high voltage charging only. Diagrams of pulse with an energy of 200 J at a load of 25, 50, 100 and 125 ohms are given in Figure 7 herein.

**Conclusions**

Considering the conducted analysis of the existing developments in the field of external defibrillation, the applicable recommendations on cardiopulmonary resuscitation, and the results of the theoretical research, we may arrive at conclusions as follows:

1. Optimal is the biphasic pulse of rectangular shape, that provides a constant current density of 14 - 16 A, delivered in 4 - 5 ms. The maintenance of these parameters can be achieved using the current stabilization technology.

2. According to the recommendations, the starting charge for adults is 150 J, with a possibility of increasing it up to 360 J. The conducted studies on the presented biphasic pulses demonstrate the possibility of achieving general repolarization with lower values of energy, but it is necessary to have an engineering solution to deliver the maximum energy of 360 J.

3. The ratios between the first phase and the second phase of the pulses in external biphasic defibrillators under consideration show significant differences, but all of them have been implemented in clinically approved defibrillators. So, we can conclude that the issue on the ratio between the phases remains on the agenda as a subject for further research.

**Statement on ethical issues**

Research involving people and/or animals is in full compliance with current national and international ethical standards.

**Conflict of interest**

None declared.

**Author contributions**

The authors read the ICMJE criteria for authorship and approved the final manuscript.
References
Polynomial filtering of low- and high- frequency noise for improving the accuracy of ECG signal processing: new advancements

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Abstract
The article describes a solution of the ECG signal processing problem in the presence of low- and high- frequency noises, which reduce the accuracy of selection of the signal informative parameters during their processing. To increase the accuracy of the signal informative parameters selection, developed is a new method for noise filtering based on a polynomial approximation of high frequency filters and wide-band reject filters using Newton polynomials. Applying the developed method of processing, analyzed is its functionality and efficiency with the use of full-scale reference ECG signal samples, and on the basis of quantitative indices, the comparison of the efficiency of the offered method in relation to the known approaches is carried out. To evaluate the noise characteristics by means of the present method some fragments of low- and high- frequency noises are selected from noise-laden ECG signal recording. It has been found that the application of the Newton polynomials to approximations of the transfer characteristics in high frequency filters and wide-band reject filters greatly increases the accuracy of the ECG signal processing analysis and attenuates noises.

Keywords
ECG signal processing, Filtering, High-frequency filter, Reject filter, Cascade of filters, Low-frequency noise, High-frequency noise, Newton polynomial, Noise attenuation, Measuring electrodes

Introduction
Nowadays, in solving the electrocardiographic data processing issues widely used are processing methods based on polynomial ECG signal filtering methods [1-9]. The topicality of the polynomial filtering methods consists in the fact that they allow us to largely adjust their parameters according to the processed ECG signal parameters, as well as improve the efficiency of processing and selecting informative ECG signal components from an additive mixture of noises.

To improve the efficiency of processing of the electrocardiographic data, at present there is a necessity to jointly consider the measuring electrodes to evaluate their quality, which determines the efficiency and reliability of the ECG signal processing analysis, in particular the means of noise filtering [10,11]. The need for such consideration is as follows. First, characteristics of contact conductive agents make their effect on the accuracy of reproduction (formation) of the signal parameters, i.e. the minimization of losses of the obtained ECG signal informative segments during the signal recording. Second, it is required to increase accuracy of the ECG signal processing means against the background of affecting noises. In case of low quality of the ECG signal recording due to the characteristics of the electrodes themselves, errors may occur, which are associated with the formation of the ECG signal informative parameters and which may be recognized in the process of noise filtering as distortions introduced by filter algorithms. All this is particularly important in the development of methods for noise filtering, as well as in the analysis and processing of long-term monitograms.

Noises, appearing in recording an ECG signal, namely the low- and high-frequency ones, are among the main factors that reduce the accuracy of ECG signal processing. When recording ECG signals, the low frequency noises occur due to a poor physical contact between a measuring electrode conductive agent and a bioobject, due to human breathing, etc. [1-3,5-8,12]. High-frequency electrical noises are generated mainly by networked external electrical devices, including such as physiotherapy and surgical equipment [1-
9,12]. Besides, high-frequency noise can also include some muscle noises appearing as a result of bioobject skeletal muscular motion activity [3,5-7,12,13].

Effects produced by the above types of noises greatly reduce the accuracy of the ECG signal analysis, in particular the measurements of signal amplitudes and the time parameters, carried out automatically or manually by a physician [14].

The low frequency noise analysis has been treated by a number of works [2-8,12,15], from which it can be noted that the ECG signal low-frequency noise is a sum of deterministic components with a frequency from 0.1 Hz to 0.3 Hz, but not more than 1 Hz, having a random amplitude.

The analysis of the high-frequency noise parameters is also the subject of several studies [2-8,12,13], from which it can be understood that the electrical noise is a narrowband deterministic signal, having slowly varying harmonics of different phases with a frequency of 50 Hz. Hence, the muscle noise is a wide-band noise with the zero mean value, overlapping with the ECG signal frequency spectrum [13,16]. The muscle noise is the most dangerous, difficultly removable noise due to high muscle activity during the signal recording. Taking into account these features of the myographic noise, in the ECG signal processing used is the so-called “rejection” approach, i.e. highly noise-laden ECG signal segments are excluded from further consideration [14].

However, despite the studies devoted to the analysis of the characteristics of affecting noises, in particular narrow-band electrical noises, at the present time, we observe a steady tendency of an interrupted growth in the noise level due to an increase in the energy consumption in all areas of activity that may lead to deterioration of the general electromagnetic background [17]. Besides, observed are high frequency electrical noises induced by laptop internal units [18]. Taking into account all the above, studies in [9] suggest that during the ECG signal recording with a laptop, when disconnecting the power cable of the latter, there may be possible generation of wide-band electrical noise induced by the laptop internal units. The frequency component of the given noise is identified as that to be close to the range from 44 Hz to 56 Hz with a noise center frequency of 50 Hz upon computing the discrete Fourier transform. The above noise, as well as a narrow-band network noise, may affect the amplitude and the time parameters of the ECG signal, in particular, the type of wave patterns of the signal RR-intervals. However, the identified wide-band noise differs from the narrowband network noise in frequency characteristics.

Reference research literature suggests that the most commonly used are filters approximated by the Butterworth polynomials, and as to other polynomials, for example, by the Chebyshev (I and II type), Bessel and Cauer, they are employed less common for elimination of the above analyzed noises, namely for removal of the low- and high-frequency ones. In papers [1-7,19] the experimental evidence shows that the Chebyshev polynomials (I, II), the Bessel and Cauer polynomials for filtering the ECG signal noises are less effective. This is due to low accuracy of the obtained ECG signal processing output results that can be attributed to generation of the greatest values of the filter’s own error based on the filter frequency characteristics. At the same time, filters based on the Butterworth polynomial are characterized by flatness and smoothness of the frequency response characteristics as compared with the other types of filters [2-8]. The Butterworth polynomials are a generally accepted form of placing the transfer function into the circular quadratics [20,21]. Also known is the application of the Newton polynomials for approximation of the transfer characteristics of the reject filters [9].

The Newton polynomials in approximations of the filter transfer characteristics are applied in view of the fact that theoretically derivable properties of the filter successfully correspond to the multi-component signals structure. The above property is extremely important in processing of complexly structured pulse signals of the cardiovascular origin that justifies the application of the Newton polynomial for solving the electrocardiographic data processing tasks, in particular, the low- and high-frequency noise filtering. It should be noted that the above polynomial is one of the members of the automatic control theory, which is currently used for the synthesis of objects in control systems and which shows the best quality results [21]. Currently, however, the application of the Newton polynomial for improving efficiency of the ECG signal processing, in particular for approximation of filtering means transfer characteristic, is less well discussed.

It is known that low-frequency noises, appearing in case of a poor contact of the conductive agents in measuring electrodes, often lies in a low frequency range of the signal, and, as a rule, high frequency filters are
used to suppress this sort of noises. At the same time, for removing high-frequency components in electrical noise, which are close to a frequency of 50 Hz, typically applied are the reject filters, the frequency characteristics of which have a dip at this frequency. In this connection, for removing the low-frequency noise it is advisable to use a high-frequency filter, since it can suppress noises in a low frequency range with minimal distortions of the ECG signal informative parameters. However, for removing electrical noise it is most reasonable to employ a reject filter, which largely eliminates the high frequency component at the frequency of the electrical noise. In approximations of the transfer characteristics in the high-frequency filters and the reject filters the Newton polynomial should be used to produce the lowest values of the filter’s own error, based on the frequency characteristics of the filter itself.

In the present paper we consider our solution of the two ECG signal processing issues based on improving the filtering accuracy. The first issue is connected with the high-frequency filtering of the low-frequency noise in the multi-lead ECG signal recording with various electrodes in long-term cardiac monitoring. The second issue is based on the reject filtering of wideband electrical noise in the single-lead ECG signal recording. To evaluate the full-scale noises in each of the treated issues applied is a method based on the noise subtraction. We have defined the two issues of filtering with availability of full-scale measurements of the ECG signal. We consider the method of high-frequency and reject filtering based on the Newton polynomials, and the accuracy of this method is compared with the well recognized Butterworth high-frequency and reject filtering.

Aims of research

The aim is to develop and study the method for filtering of low- and high-frequency noise for improving the accuracy of ECG signal processing.

Materials and methods

Materials used in our studies have been the recorded reference noise-laden samples produced with multi-lead ECG signal recording in a human using 12-lead Holter monitor KARDIOTECHNIKA-07-3/12, manufactured by INCART Company, available at the National Medical Research Center of V.A. Almazov. To evaluate the characteristics of low-frequency noise, the reference noise-laden samples of the multi-lead ECG signal have been recorded with 4 types of different electrodes designed for long-term cardiac monitoring. To record the signals to be assessed, selected have been the following widely used models of wet electrodes: H925G, H995G, MSGLT-05MGRT and M2202A [11]. At the same time, in order to take into account the nature of occurrence of the low frequency noise, namely, the noise amplitude fluctuation, each multi-lead ECG signal recording has been produced in such a manner so that it has contained more than 80 cardiac cycles.

The noise-laden sample of the ECG signal produced with single-lead recording has been obtained using the multifunction measuring system of bioelectrical signals MITSAR EEG-202, manufactured by MITSAR DIAGNOSTICS SOLUTIONS Co., at the Research Institute of Cardiological Techniques (INCART). Besides, in order to take into account the deterministic frequency noise [9], the recorded single-lead noise-laden ECG signal has covered more than 20 cardiac cycles.

Formulation of the study issue

Issue 1.

The issue of processing of multi-lead signal recording is primarily associated with the proper separation of the informative components $\hat{S}(q)$ from an additive mixture containing an ECG signal and low-frequency noise $\hat{n}(q)$, that is interpreted in the form of (1). Defined is the issue of separating of informative signal $\hat{S}(q)$ with high-frequency filtering of the analyzed signal $x(q)$ from distorting low-frequency noises $\hat{n}(q)$. Separating of the low-frequency noise in the i-th lead from the analyzed noise-laden ECG signal records $x(q)$ of form (1) was carried out with a method based on the subtraction of noise $\hat{n}(q)$ of form (2) from the noise-laden recording $x(q)$ and the filtered informative component of the ECG signal $\hat{S}(q)$.

$$x_i(q) = \hat{n}(q) + \hat{S}(q),$$

$$\hat{n}(q) = x_i(q) - \hat{S}(q),$$

where $q$ – measurement readings, $i$ – lead of the ECG signal in multi-lead recording.

Issue 2.

Similarly to issue 1, for processing of the single-lead signal recording formulated is another issue of separating of the informative components $\hat{S}(q)$ from an additive mixture of an ECG signal and wide-band noise $\hat{n}(q)$, that is interpreted in the form of (3). Separating the wide-band electrical noise from the analyzed single-lead ECG signal record $x(q)$ of form (3) was
carried out by the method based on the subtraction of noise \( \tilde{n}(q) \) of form (4) from the noise-laden recording \( x(q) \) and the filtered informative component ECG signal \( S(q) \).

\[
\begin{align*}
\frac{\tilde{n}(q)}{x(q)} &= \frac{\tilde{S}(q)}{S(q)}, \\
\tilde{n}(q) &= x(q) - \tilde{S}(q),
\end{align*}
\]

where \( q \) – measurement readings.

To configure the high frequency filter (HFF) parameters, selected has been an edge frequency equal to 1 Hz, according to \([8, 22]\). The advisability of selecting the given frequency is that at a frequency of 1 Hz, using the method of frequency selection, experimentally established is a maximum low-frequency noise reduction with minimum distortions in the ECG signal parameters, therefore it is reasonable to use this frequency for filtering. The wide-band reject filter (RF) is configured for an identified frequency of electric noise \([9]\), namely in the range from 44Hz to 56Hz. Besides, selected is sampling frequency \( f_D = 250 \text{ Hz} \) \([23, 24]\). The selection of the above sampling frequency is determined by the fact that it is just this frequency that is intended for the ECG signal processing to improve the accuracy of the signal parameters measurement \([23, 24]\). Using the selected values in the normalized frequency range with the help of transfer functions of continuous analogue filters, calculated are the HFF and RF transfer functions for the Newton and Butterworth polynomials, taking into account (5) \([25]\).

\[
\omega_{cl_2} = \left( \frac{f_{cl_2}}{f_D} \right) \cdot 2\pi, \Omega_{cl_2} = \left( \frac{2}{T} \right) \Omega_{cl_2}, \quad \Omega_c = \sqrt{\Omega_{cl_1} \cdot \Omega_{cl_2}},
\]

where \( \omega_{cl_2}, \Omega_{cl_2} \) – is the lower and upper limit of the edge frequency for calculation of the reject filter, \( \Omega_c \) is a center frequency of the filter edge.

In the synthesis of HFF selected are the Newton and Butterworth polynomials of the second order \([20]\) to simplify the calculations in the synthesis of the filters and avoid distortions of the ECG signal parameters induced by high order filters \([8, 22]\). In the synthesis of a wide-band RF, the Newton and Butterworth polynomials of the first and second orders are selected taking into account that the transformation of the normalized analogue filter parameters is accompanied by doubling of the continuous transfer function order in the reject filters \([9, 25]\). To cascade the wide-band reject filters used are the transfer functions of the second and fourth order, obtained with the Newton and Butterworth polynomials of the first and second order, respectively.

It should be noted in this case that the Newton and Butterworth polynomials of the first order coincide with each other \([20]\), and therefore the wide-band RF transfer functions of the second order are identical.

The transformation of continuous filter transfer function \( W(s) \) into discrete function \( W(z) \) has been carried out by bilinear transformation in the MATLAB software environment. The transformation has been performed using function bilinear () as

\[
s = \frac{2}{T} \left( \frac{1-z^{-1}}{1+z^{-1}} \right)
\]

at \( T=1s \).

The calculated continuous and discrete transfer function in the Newton (6) and Butterworth (7) HFF are shown below.

\[
\begin{align*}
W(s) &= \frac{s^2}{s^2 + 0.0502426s + 0.00063108} \\
W(z) &= \frac{0.975z^2 - 1.951z + 0.975}{z^2 - 1.95z + 0.951} \\
W(s) &= \frac{s^2}{s^2 + 0.035521s + 0.00063108} \\
W(z) &= \frac{0.9824z^2 - 1.965z + 0.9824}{z^2 - 1.964z + 0.9651}
\end{align*}
\]

The calculated continuous and discrete transfer function in the Newton (8) and Butterworth (9) cascade wide-band RF are given below.

For correction of phase distortions introduced by the above synthesized polynomial filters, the filtered signal has been repeatedly passed through the same filter, but in the reverse order. In case of such an implementation, the resulting phase distortions are mutually compensated, and the resulting phase shift is equal to zero for the entire frequency component of ECG signal. This form of the filters implementation in the theory of digital signal processing is known as a bi-directional filtering technique \([26]\). Figures 1 and 2 show diagrams of implementation of bi-directional high-frequency and wide-band reject filters for processing the ECG signal.

In case of the bi-directional filter technique, the input sequence of readings \( x[n] \) in a noise-laden signal is processed through the HFF \( z[n] \) in the forward direction, then using the time inversion (TI) unit the order of the readings \( w[n] \) sequence is reversed. Hence, \( w[n] \) readings are filtered in the reverse direc-
tion \(v[n]\) using HFF, then the final time inversion (init TI) reverses the order of the readings sequence. As a result, the appeared shifts are mutually compensated.

Similarly implemented is the bi-directional cascade of wide-band reject filters, the diagram of which is presented in Figure 2 herein.

In case of the bi-directional implementation of a wide-band RF cascade, it differs considerably from the bi-directional implementation of HFF. There is a need for a double implementation of each cascade of the wide-band RF. In the present diagram, noise-laden signal \(x[n]\) is processed with the wide-band RF of the first sequence for suppression of noises and separation of signal \(s_1[n]\) at the filter output, and then the processed signal is delivered to the input of the wide-band RF second sequence to suppress the residual noise and separate the clean signal \(s_2[n]\). In Figure 2 herein, the wide-band RF of the second order is designated as “filter 1” and that of fourth order as “filter 2”.

Convolution of the bi-directional HFF implementation in the frequency domain is represented in formula (10), and the wide-band RF cascade in formula (11).

\[
W_1(s) = \frac{s^2 + 2,094}{s^2 + 0,463s + 2,094}
\]
\[
W_1(z) = \frac{0,8681z^2 - 0,5427z + 0,8681}{z^2 - 0,5427z + 0,7362}
\]
\[
W_2(s) = \frac{s^4 + 4,189s^2 + 4,388}{s^4 + 0,926s^3 + 4,404s^2 + 1,940s + 4,388}
\]
\[
W_2(z) = \frac{0,7536z^4 - 0,9422z^3 + 1,802z^2 - 0,9422z + 0,7536}{z^4 - 1,085z^3 + 1,767z^2 - 0,799z + 0,542}
\]
\[
W_3(s) = \frac{s^6 + 6,284s^4 + 13,166s^2 + 9,194}{s^6 + 1,389s^5 + 6,928s^4 + 5,919s^3 + 14,513s^2 + 6,096s + 9,194}
\]
\[
W_3(z) = \frac{0,6542z^6 - 1,277z^5 + 2,73z^4 - 2,614z^3 + 2,73z^2 - 1,277z - 0,6542}{z^6 - 1,628z^5 + 3,092z^4 - 2,557z^3 + 2,277z^2 - 0,8825z + 0,399}
\]
\[
W_4(s) = \frac{s^2 + 2,094}{s^2 + 0,463s + 2,094}
\]
\[
W_4(z) = \frac{0,8681z^2 - 0,5427z + 0,8681}{z^2 - 0,5427z + 0,7362}
\]
\[
W_5(s) = \frac{s^4 + 4,189s^2 + 4,388}{s^4 + 0,654s^3 + 4,404s^2 + 1,371s + 4,388}
\]
\[
W_5(z) = \frac{0,8078z^4 - 1,01z^3 + 1,931z^2 - 1,01z + 0,8078}{z^4 - 1,118z^3 + 1,894z^2 - 0,9015z + 0,6529}
\]
\[
W_6(s) = \frac{s^6 + 6,284s^4 + 13,166s^2 + 9,194}{s^6 + 1,117s^5 + 6,802s^4 + 4,782s^3 + 14,250s^2 + 4,905s + 9,194}
\]
\[
W_6(z) = \frac{0,7012z^6 - 1,315z^5 + 2,926z^4 - 2,802z^3 + 2,926z^2 - 1,315z - 0,7012}{z^6 - 1,661z^5 + 3,237z^4 - 2,753z^3 + 2,536z^2 - 1,018z + 0,4806}
\]
From above formulas (10) and (11) we can conclude that in case of bi-directional implementing of each of the filters, their order is doubled. Theoretically, doubling of the filter order in the bi-directional filter implementation concept leads to the fact that the resulting suppression in the band of noise retaining at the frequency characteristic will increase by two times [26].

An evaluation of the high-frequency and wideband RF filters application efficiency is based on their quantitative indices. For the above evaluation calculated are the values of experimental root-mean-square deviation (RMSD) of the signal readings and the separated noise when filtering (12), as well as the noise attenuation coefficient (NAC) according to [26].

\[
CKO = \sqrt{\frac{1}{N-1} \sum_{i=1}^{N} (n_i - \mu)^2} \\
\mu = \frac{1}{N} \sum_{i=1}^{N} n_i
\]  

(12)

\[
\text{KOP} = 20 \log_{10} \left( \frac{A_{out}}{A_{in}} \right),
\]

where \( N \) – number of readings, \( n_i \) – readings, \( \mu \) – mean value of readings, \( A_{out} \) and \( A_{in} \) – root-mean-square value of amplitude of output (filtered) and input (noise-laden) signal readings.

The calculated RMSD values of the filtered signals and separated noises, in the form of a box plot for RMSD values, have been graphically represented with Python Graphing Library, Plotly [27].

Results
Based on the above calculated transfer characteristics of the filters, we have obtained the results of the ECG signal processing when filtering the low- and high-frequency noise as outlined below.

Low-frequency noise filtering in the multi-lead recorded ECG signal
Our analysis of the obtained results makes possible to support our statement that the Newton-Butterworth synthesized high-frequency filters, tuned to an edge frequency of 1 Hz, are capable to provide filtering out low-frequency noise with minimal distortions in informative regions and thereby separating the low frequency drift of an ECG signal. As an example, Figure 3 shows the result of the initial ECG signal of the fourth precordial V4 lead in multi-lead recording containing low frequency noise, and the result of the noise separation by means of the high-frequency filter on the basis of the Newton and Butterworth polynomials. For better visualization, the ECG signal processing results in Figure 3 are scaled for the 5th cardiac cycle by the Newton and Butterworth filters (a); in (b) illustrated are the results of low-frequency noise separation.

Results of the quantitative indices calculation for 12 different ECG signal recording, covering more than 80 cardiac cycles, are presented in Table 1 herein.

Our analysis of the quantitative results shows that the HFF based on the Newton polynomial generates least the signal’s RMSD value, when filtering, maximally separates the low frequency drift and to the highest degree attenuates low-frequency noises as compared
with the Butterworth filter, that confirms the effectiveness of the Newton polynomial in enhancing the ECG signal processing accuracy under the influence of the given noise.

Filtering of wide-band electrical noise in the single-lead recorded ECG signal

We have obtained the ECG signal filtering results with the use of synthesized transfer functions of the Newton and Butterworth wide-band RF. Our result of the wide-band electrical noise filtering of the single-lead recorded ECG signal is given in Figure 4 herein.

Using the calculated transfer functions of wide-band RF (8), (9), in case of their bi-directional implementation (11), identified are quantitative indices, characterizing the quality of the ECG signal processing. Our analysis of the quality of the wide-band electrical noise suppressing has been performed with several methods of filters connection, namely, a typical sequence without cascade (n = 2, n = 4), a cascade form (n = 2 and n = 4) and with general transfer function of cascade filter (n = 6). The results of the quantitative indices calculation are presented in Table 2 herein.

Our analysis of the presented results shows that the cascade of wide-band Newton polynomial RF to the least degree rejects the filtering results, maximally separates the noises and to the highest degree attenuates high-frequency noises in comparison with the Butterworth filter that also confirms the effectiveness of the Newton polynomial application in enhancing the ECG signal processing efficiency.

Basing on the ECG signal filtering results, obtained in single- and multi-lead signal recording, we note that the use of Newton polynomials in approximations of the filter transfer characteristics increases the accuracy in filtering of low- and high-frequency noises. Meanwhile, the use of the Butterworth filters for suppression of low- and high-frequency noise also allows attenuating noises and separating the required signal informative parameters. The efficiency of the Newton filters in comparison with Butterworth ones is that they produce the lowest values of their own errors during the ECG signal processing. Figure 5 gives a Tukey diagram showing accuracy of the ECG signal processing with two methods of the low-frequency noise filtering.

At the same time, the analysis of the quantitative indices, namely the low- and high-frequency attenuation coefficient, obtained when processing the multi- and single-lead ECG signal recordings, shows a negative value. The negative value of the above index is determined by the lowest value of the filtered ECG signal amplitude in relation to the noise-laden (input) signal, so this index is expressed as a negative number. The lower is the index value in filtering, the better the filter attenuates noise and the more resistant to noises the ECG signal becomes. In comparison with the Butterworth filter results, the NAC index values are lower in the Newton filter, i.e. the Newton filter best
Table 1. Evaluation of low-frequency noise filtering quality

<table>
<thead>
<tr>
<th>Lead / Filter</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>V5</th>
<th>V6</th>
<th>I</th>
<th>III</th>
<th>aVR</th>
<th>aVF</th>
<th>II</th>
<th>aVL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newton high-frequency filter</td>
<td><strong>77.4</strong></td>
<td><strong>343.9</strong></td>
<td><strong>251.4</strong></td>
<td><strong>212.6</strong></td>
<td><strong>150.6</strong></td>
<td><strong>119.4</strong></td>
<td><strong>58.1</strong></td>
<td><strong>185.9</strong></td>
<td><strong>94.9</strong></td>
<td><strong>180</strong></td>
<td><strong>178.6</strong></td>
<td><strong>104.9</strong></td>
</tr>
<tr>
<td>RMSD, mcV S(q)</td>
<td><strong>343.9</strong></td>
<td><strong>251.4</strong></td>
<td><strong>212.6</strong></td>
<td><strong>150.6</strong></td>
<td><strong>119.4</strong></td>
<td><strong>58.1</strong></td>
<td><strong>185.9</strong></td>
<td><strong>94.9</strong></td>
<td><strong>180</strong></td>
<td><strong>178.6</strong></td>
<td><strong>104.9</strong></td>
<td></td>
</tr>
<tr>
<td><strong>92.4</strong></td>
<td><strong>376.3</strong></td>
<td><strong>251.8</strong></td>
<td><strong>226.9</strong></td>
<td><strong>146</strong></td>
<td><strong>102</strong></td>
<td><strong>61.4</strong></td>
<td><strong>190</strong></td>
<td><strong>99.4</strong></td>
<td><strong>184.8</strong></td>
<td><strong>184.6</strong></td>
<td><strong>106.9</strong></td>
<td></td>
</tr>
<tr>
<td><strong>84.5</strong></td>
<td><strong>371.1</strong></td>
<td><strong>243.2</strong></td>
<td><strong>230.6</strong></td>
<td><strong>158.1</strong></td>
<td><strong>107.3</strong></td>
<td><strong>59.7</strong></td>
<td><strong>188.7</strong></td>
<td><strong>101.1</strong></td>
<td><strong>185.1</strong></td>
<td><strong>186.3</strong></td>
<td><strong>104.4</strong></td>
<td></td>
</tr>
<tr>
<td>RMSD, mcV n(q)</td>
<td><strong>719.8</strong></td>
<td><strong>296.9</strong></td>
<td><strong>1086</strong></td>
<td><strong>808.4</strong></td>
<td><strong>790.3</strong></td>
<td><strong>626.7</strong></td>
<td><strong>368.8</strong></td>
<td><strong>1717.4</strong></td>
<td><strong>1235.6</strong></td>
<td><strong>1899.3</strong></td>
<td><strong>2081.6</strong></td>
<td><strong>677.9</strong></td>
</tr>
<tr>
<td><strong>808.0</strong></td>
<td><strong>952.8</strong></td>
<td><strong>1752.6</strong></td>
<td><strong>1499.6</strong></td>
<td><strong>1867.7</strong></td>
<td><strong>1501.6</strong></td>
<td><strong>625.2</strong></td>
<td><strong>1444.9</strong></td>
<td><strong>1379.6</strong></td>
<td><strong>621.4</strong></td>
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<td></td>
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<tr>
<td><strong>215</strong></td>
<td><strong>257.8</strong></td>
<td><strong>395.3</strong></td>
<td><strong>328.1</strong></td>
<td><strong>449.3</strong></td>
<td><strong>617.7</strong></td>
<td><strong>149.4</strong></td>
<td><strong>69.1</strong></td>
<td><strong>174</strong></td>
<td><strong>130.9</strong></td>
<td><strong>58.2</strong></td>
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<tr>
<td><strong>207</strong></td>
<td><strong>201</strong></td>
<td><strong>565.9</strong></td>
<td><strong>422.8</strong></td>
<td><strong>424.8</strong></td>
<td><strong>388.8</strong></td>
<td><strong>103.2</strong></td>
<td><strong>963.5</strong></td>
<td><strong>494.9</strong></td>
<td><strong>966</strong></td>
<td><strong>971.2</strong></td>
<td><strong>483.4</strong></td>
<td></td>
</tr>
<tr>
<td>Butterworth high-frequency filter</td>
<td><strong>81.4</strong></td>
<td><strong>396.6</strong></td>
<td><strong>303.4</strong></td>
<td><strong>237.1</strong></td>
<td><strong>167</strong></td>
<td><strong>132.7</strong></td>
<td><strong>68.8</strong></td>
<td><strong>197</strong></td>
<td><strong>110.2</strong></td>
<td><strong>194.2</strong></td>
<td><strong>197.4</strong></td>
<td><strong>109.7</strong></td>
</tr>
<tr>
<td>RMSD, mcV S(q)</td>
<td><strong>396.6</strong></td>
<td><strong>303.4</strong></td>
<td><strong>237.1</strong></td>
<td><strong>167</strong></td>
<td><strong>132.7</strong></td>
<td><strong>68.8</strong></td>
<td><strong>197</strong></td>
<td><strong>110.2</strong></td>
<td><strong>194.2</strong></td>
<td><strong>197.4</strong></td>
<td><strong>109.7</strong></td>
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</tr>
<tr>
<td><strong>97.9</strong></td>
<td><strong>433.7</strong></td>
<td><strong>310.4</strong></td>
<td><strong>253.5</strong></td>
<td><strong>160.9</strong></td>
<td><strong>112.8</strong></td>
<td><strong>73.1</strong></td>
<td><strong>197.9</strong></td>
<td><strong>113.4</strong></td>
<td><strong>195.6</strong></td>
<td><strong>200</strong></td>
<td><strong>110.7</strong></td>
<td></td>
</tr>
<tr>
<td><strong>214.4</strong></td>
<td><strong>229.8</strong></td>
<td><strong>380.7</strong></td>
<td><strong>424.7</strong></td>
<td><strong>447.9</strong></td>
<td><strong>617.2</strong></td>
<td><strong>147.8</strong></td>
<td><strong>64.9</strong></td>
<td><strong>171.4</strong></td>
<td><strong>127.1</strong></td>
<td><strong>197.6</strong></td>
<td><strong>57.1</strong></td>
<td></td>
</tr>
<tr>
<td>RMSD, mcV n(q)</td>
<td><strong>719.5</strong></td>
<td><strong>273.2</strong></td>
<td><strong>1080.7</strong></td>
<td><strong>803.9</strong></td>
<td><strong>789.2</strong></td>
<td><strong>625.9</strong></td>
<td><strong>368.3</strong></td>
<td><strong>1712</strong></td>
<td><strong>1232.2</strong></td>
<td><strong>1899</strong></td>
<td><strong>2081.2</strong></td>
<td><strong>677.9</strong></td>
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<tr>
<td><strong>807.9</strong></td>
<td><strong>944.8</strong></td>
<td><strong>1749.3</strong></td>
<td><strong>1498.7</strong></td>
<td><strong>1867.3</strong></td>
<td><strong>1501.6</strong></td>
<td><strong>625.2</strong></td>
<td><strong>1444.6</strong></td>
<td><strong>1379.1</strong></td>
<td><strong>621.4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>206.3</strong></td>
<td><strong>164.1</strong></td>
<td><strong>555</strong></td>
<td><strong>416.2</strong></td>
<td><strong>422.1</strong></td>
<td><strong>387.4</strong></td>
<td><strong>100.9</strong></td>
<td><strong>963</strong></td>
<td><strong>494.9</strong></td>
<td><strong>965.1</strong></td>
<td><strong>970</strong></td>
<td><strong>483.4</strong></td>
<td></td>
</tr>
<tr>
<td>NAC, dB</td>
<td><strong>-39</strong></td>
<td><strong>-22.2</strong></td>
<td><strong>-28.3</strong></td>
<td><strong>-25.9</strong></td>
<td><strong>-32.9</strong></td>
<td><strong>-35.5</strong></td>
<td><strong>-41</strong></td>
<td><strong>-34.5</strong></td>
<td><strong>-28.1</strong></td>
<td><strong>-30.9</strong></td>
<td><strong>-24.8</strong></td>
<td><strong>-38.3</strong></td>
</tr>
<tr>
<td><strong>-35</strong></td>
<td><strong>-25.9</strong></td>
<td><strong>-33</strong></td>
<td><strong>-34.2</strong></td>
<td><strong>-39.9</strong></td>
<td><strong>-40.2</strong></td>
<td><strong>-40.6</strong></td>
<td><strong>-32.7</strong></td>
<td><strong>-29.3</strong></td>
<td><strong>-28.6</strong></td>
<td><strong>-20.7</strong></td>
<td><strong>-36.6</strong></td>
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</tr>
<tr>
<td><strong>-25</strong></td>
<td><strong>-25.6</strong></td>
<td><strong>-26.8</strong></td>
<td><strong>-31.9</strong></td>
<td><strong>-30.1</strong></td>
<td><strong>-24.6</strong></td>
<td><strong>-39.8</strong></td>
<td><strong>-31.6</strong></td>
<td><strong>-27.6</strong></td>
<td><strong>-27.2</strong></td>
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<tr>
<td><strong>-27.6</strong></td>
<td><strong>-22.8</strong></td>
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<td><strong>-26.3</strong></td>
<td><strong>-30.6</strong></td>
<td><strong>-36</strong></td>
<td><strong>-32.1</strong></td>
<td><strong>-32.6</strong></td>
<td><strong>-32.5</strong></td>
<td><strong>-31</strong></td>
<td><strong>-34.7</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Designations of quantitative ECG signal processing results for electrodes:
* - H92SG, ** - H99SG, *** - MSGLT-05MGRT, **** - M2202A

The results of the low-frequency noise separation and their calculated RMSD value, generated by using the filters, show that the H92SG and H99SG electrodes generate the highest RMSD noise value as compared to electrodes MSGLT-05MGRT and M2202A.

of all attenuates the low- and high- frequency noises. Figure 6 offers a Tukey diagram showing an accuracy of the low-frequency noise attenuation coefficient calculation.

Our analysis of the quantitative results of multi-lead ECG signal recording processing, with various electrodes, allows us to note that a minor variability is available between the RMSD values in the filtered signals of the same ECG signal lead, however, due to nonstationarity of the signal parameters, some insignificant differences exist. Despite the above features, the results of the low-frequency noise separation and their calculated RMSD value, generated by using the filters, show that the H92SG and H99SG electrodes generate the highest RMSD noise value as compared to electrodes MSGLT-05MGRT and M2202A. Electrode MSGLT-05MGRT generates the lowest RMSD value in 7 of 12 analyzed ECG signal leads, while
Figure 4. Filtering of the ECG signal wide-band electrical noise

Table 2. Evaluation of the high-frequency noise filtering quality

<table>
<thead>
<tr>
<th>No</th>
<th>Type of reject filter implementation</th>
<th>The polynomial reject filter</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Newton</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RMSD, mV</td>
<td>RMSD, mV</td>
<td>NAC, dB</td>
<td>RMSD, mV</td>
<td>RMSD, mV</td>
</tr>
<tr>
<td>1</td>
<td>The first RF output, n=2.</td>
<td>178,719</td>
<td>15,100</td>
<td>-0,0295</td>
<td>178,719</td>
<td>15,100</td>
</tr>
<tr>
<td>2</td>
<td>The second RF output, n=4 without n=2.</td>
<td>178,548</td>
<td>15,307</td>
<td>-0,0367</td>
<td>178,886</td>
<td>15,246</td>
</tr>
<tr>
<td>3</td>
<td>Cascade n=2 and n=4.</td>
<td>178,380</td>
<td>15,373</td>
<td>-0,0430</td>
<td>178,716</td>
<td>15,322</td>
</tr>
<tr>
<td>4</td>
<td>With general transfer function of cascade n=6.</td>
<td>178,386</td>
<td>15,373</td>
<td>-0,0422</td>
<td>178,723</td>
<td>15,322</td>
</tr>
</tbody>
</table>

The results of multi-lead ECG signal recording processing show a minor variability in the RMSD values in the filtered signals of the same ECG signal lead, taken with different electrodes, a high variability is demonstrated in RMSD values of the separated noises. The high variability in RMSD noise values let us conclude that electrodes H92SG, H99SG, MSGLT-05MGRT and M2202A, to varying degrees, generate low-frequency noises.

electrode M2202A generates the lowest value only in 5 of 12. Figure 7 gives a diagram Tukey showing an accuracy of the low-frequency noise separation generated by different electrodes in multi-lead ECG signal recording.

Systematizing the results of multi-lead ECG signal recording processing, we can note that despite a minor
caused by potentials of electrodes polarization, when recording bioelectric cardiac potentials. Assessing the RMSD noise value, we can state that the Newton synthesized high-frequency filter allows us to largely attenuate low-frequency noises generated by the various measuring electrodes. Besides, the presented Tukey diagram shows that electrode MSGLT-05MGRT has much lower RMSD value of the separated noise than other analyzed electrodes.

Previously, in work [11] it was stated that the MSGLT-05MGRT electrode demonstrated a high probability of the true ECG signal parameters recording, in particular it is applicable to low amplitude P waves. The above feature was associated with low electrical resistance in the ECG signal electrodes' solid contact conductive agents. In electrodes H92SG and H99SG detected was a high electrical resistance of CCA, affecting an accuracy of the signal parameters recording. It has been identified that in electrode M2202A, in case of long-term cardiac parameters monitoring, liquid CCA flows and exits the measuring cell specified area that reduces an accuracy of the signal recording [11].

The quantitative analysis of the results of single-lead ECG signal processing shows that in case of the cascade (sequence) connection of wide-band RF at the output of each designed sequence the RMSD value of the filtered signal is greatly reduced and attenuates noise. However, despite that, in case of the sequential implementation of the reject filters and the implementation with a general transfer function of the used filters cascade, the RMSD values of the separated noise are the same. The above feature becomes apparent not only when using the Newton reject filters, but also the Butterworth filters. This is due to the fact that in case of the sequential connection of the selected order reject filters, the filtered ECG signal value is generated at the output of the filters cascade. Hence, when using the general transfer function of the reject filters, obtained as a product by two reject filters, the ECG signal value is generated at the output of the filter with general transfer function. All the above allows us to conclude that the use of the wide-band reject filters of the cascade structure makes it possible to increase an accuracy of the ECG signal processing (Figure 8 herein). Figure 8 shows a histogram of ECG signal processing quantitative results by indices of filtered signal RMSD and the high frequency noise attenuation.
Significant data have been obtained using the results of the ECG signal single- and multi-lead filtering. Basing on the above data, we can conclude that the Newton high-frequency and cascade reject filters greatly increase an accuracy of ECG signal processing. These findings are supported by evidence data produced by filtering of the full-scale reference samples of noise-laden ECG signal recordings, as well as quantitative assessment of indices characterizing the quality of the ECG signal processing.

Conclusions

Our paper offers two methods for ECG signal processing developed by us. The first method is based on the use of the Newton high-frequency filter designed for increasing the accuracy of the ECG signal parameters separation at low-frequency noises. The second method is based on the application of the Newton cascade wide-band reject filters for improving the accuracy of the ECG signal parameters separation at high-frequency electrical noises.

In order to evaluate the efficiency of the developed filtering methods, recorded have been noise-laden samples of multi- and single-lead ECG signals. Calculated are the quantitative results, characterizing the signal filtering quality when ECG signal processing. The obtained results of the quantitative indices calculation confirm an increase in the ECG signal processing accuracy in comparison with the known solutions.

Funding

The research is supported by the Russian Federation Government (Grant 08-08).

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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Review of the recommender systems application in cardiology

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Abstract
The article provides a review of the recommender systems application in medical field, cardiology, in particular. The concept of recommender systems is defined, the brief history of the recommender systems development is given. The main types of recommender systems and principles of their construction are presented. The advantages and disadvantages of the recommender system methods application in cardiology are identified. Methods for improving the recommender systems are proposed.

Keywords
Recommender system, Filtering, Collaborative, Content, Hybrid, information retrieval, MRS, PEHC

Imprint

Topicality of the research
This paper presents a review of the currently available research in the field of big data, namely, software systems, called recommender systems. To date, the processing of big data, in particular, the construction of recommender systems, is one of the most promising areas of informatics development. One of the fastest growing segments of the recommender algorithms application is the segment of medicine and public health. This review is relevant also on this basis. Novelty and fundamental difference of this review is its focus on the implementation of the recommendations in the narrower, but the most important branch of medicine, cardiology.

Introduction
It is not a secret that in recent years the Internet has developed by leaps and bounds: it generates vast amounts of data stored. The average user has to process, analyze and organize the data, and, above all, allocate the necessary information from the mass. Of course, it is very difficult to do, because the necessary information is lost among the large amounts of data. In connection with this, there are tools that can assist the user in finding relevant data. These tools are called recommender systems. Recommender system is a software that analyzes users requests to predict what kind of information will be of interest to a particular user at a particular time. Recommender systems show preference of the content for a particular user based on the information that the user considers relevant or based on the processing of user’s data, such as his search queries. Recommender system made significant changes in the interaction with users. Instead of the generation of static data, the system changes, adjusts to the specific user [1]. Recommender systems have the following common characteristics: the system adapts to the individual user; takes into account the current end-user preferences, adjusting to them over time; constantly finds new information and offers it to the user. Due to these properties, sites, based on the use of recommender systems, are attractive to the user. Accordingly, recommender systems are interesting to the owners of the sites themselves, because with their help they increase the attractiveness of the site and its content. Recommender systems have been applied in many areas of human life: search for information, commerce, social networks, medicine, etc.

The main “actors” in any recommender systems are user and item, i.e. the recipient of the recommendations and the recommendation itself, i.e. the object, recommended to the user.

The user is also a source of data about his preferences, on the basis of which the item is selected [2]. In general, the task of the recommender systems can be formulated as the "definition of the object, previously unknown to the user (or not used by him for any
length of time), but useful or interesting to him in the current context”. The user’s preferences can be determined by analyzing his past behavior, i.e. grades given by the user, his preferred items. Also, no less important is the behavior of other users in the system.

**History of the recommender systems development**

The field of recommender systems is relatively new, but, despite this, conducted have been a lot of research, published numerous papers and scientific articles and developed a large number of algorithms. Recommender systems have been actively studied in the early nineties of the twentieth century, that is, since the first development in the field of collaborative filtering [1-3]. The term “recommender system based on collaborative filtering” was first used by David Goldberg in 1992, in article «Using collaborative filtering to weave an information tapestry» [4] in the process of working on the Tapestry recommender system for Xerox. The basis for the works on the content-based filtering can be considered in [5]. In subsequent years, one of the fundamental works in the field of recommender systems was written, which is also a reference: Recommender Systems Handbook [6]. This book systematizes all the different methods and concepts used in recommender systems, and related to a variety of areas of expertise, such as: data analysis, statistics, probability theory, decision support systems, marketing, and others. The book also addresses practical approaches to the construction of recommendations used in advanced corporations, for example, Amazon, Google, AT & T. Among the most important works devoted to the development of the recommender systems industry manuscript “Recommender Systems: The Textbook” [7] Can be distinguished. It lists the fundamental recommender algorithms and methods to assess their accuracy and speed. The paper details the application of recommender systems in a wide range of application areas: social systems, Internet commerce, search of the necessary information, and many others. In addition, it examines the following technical issues of the recommender systems creation: ensuring reliability and protection of information, correct ranking of results. In 2001 the manuscript was published, in which the recommender systems were first used for the selection of music. In the music recommendations, as well as in other ones, primarily the standard filtering methods are used, i.e., collaborative and content-based filtering [8]. But apart from them it is worth paying attention to the study of the hybrid approaches [9] in creating playlists, music social networking and tagging.

Wide practical application of recommender systems were not so long ago, at the end of the XX century, and it is connected primarily with the development of the Internet. But the theoretical foundation was developed long before, in the late 40-s - beginning of the 50s, and was based on machine learning. First of all, examined were self-learning algorithms, developed their mathematical foundation and built the models, which are used in recommender systems to this day. In the end of the twentieth century the collaborative filtering has been applied as a solution to deal with the excess of information on the web [10]. Tapestry (experimental postal service) [4] became one of the first systems using this approach: it allows the user to manually create queries based on the opinions or actions of other users. Taking into account the views of other participants, users were able to determine the relevance of such posts for themselves, although, of course, the creation of an additional request took more time and required certain actions from the user. Then, appeared the systems which independently collect relevant opinions and summarize them to make recommendations. For example, in a software component GroupLens [11] this technique was used to identify the materials in Usenet network that might be of interest to a particular user. Users are invited to assess the materials, and the system, in turn, brings them together with grades of other users to provide personalized results. With the development of machine learning and information retrieval, more in-depth study of the problems of interaction between human and machine, recommender systems are becoming increasingly popular. As a result, they have been increasingly applied in music, movies and lots of other products. Recommender systems more and more often appear outside the information technology industry, for example, in trade, as a way of increasing the number of sales.

In the late nineties, commercial recommender systems appeared on the market. Probably the best known of these products developer was the Amazon company [12]. Interest of the user to a particular item was calculated based on purchase history and views of the user, as well as the products viewed by him at a given time. After that, many other commercial companies have started to implement recommender systems, and some
companies have even made the implementation of recommender systems its core business. In 2006, the Netflix company launched a competition named Netflix Prize, the purpose of which was to create an algorithm of recommendations that could improve the outcome of the current internal algorithm CineMatch in tests by 10% [13]. It attracted interest in the widespread use of recommender systems and triggered activity, both in academic circles and among commercial developers. The winner was promised 1 million US dollars, that shows the importance of recommender systems for the sphere of information technologies. At the same time, Google has developed its own system of news recommendations, Google News. The system processes the history of clicks made by users, and provides a recommendation for a particular user. In the case of Google News, news stories are regarded as objects of interest, and user clicks as an assignment of a positive rating to the news story. To the collected in such a way grades the collaborative filtering algorithm is applied, and based on the output data, a decision is made to recommend one or another material to a specific user.

The beginning of the 21st century is characterized by explosive growth in popularity of social networks. Naturally, recommender systems have been applied in them. Facebook has first implemented the recommendations of potential social relations algorithms. Such recommendations are somewhat different from the product recommendations: social networking is largely dependent on its growth to increase advertising revenue, so the recommendation of potential friends provide fast growth and network connectivity. This problem is also called a prediction of references in the analysis of network graphs. Therefore, the nature of this type of algorithms is somewhat different from the standard recommendation algorithms, but, in general, the essence remains the same.

Classification of recommender systems

There are three main types of recommender systems: collaborative, content-based, and hybrid systems.

Collaborative filtering primarily analyzes user behavior in the past. Data on rates made by the user to any items, form the basis for collaborative recommender systems. At the same time, the type of rated items does not matter, important is the similarity to user preferences (although some of the characteristics of items can be considered). The method is based on the assumption that users are typically constant in their rates, i.e. if they rated the item in a certain way in the past, they will continue to rate this item as well in the future. Predictions are made individually for each user, while processed are data of multiple users. These predictions show the extent to which the user is interested in the items which have not been rated by him so far [14, 15-20].

The method of collaborative filtering, in turn, can be divided into 2 submethods (approaches):
1. user-based, i.e., “based on the neighborhood”
2. item-based, i.e., “model-based”

The user-based approach historically is the first and still used in most systems. When using the user-based for an individual user selected is the group of users similar to him. In the selection of recommendations for a given user taken into account is a combination of weights and rates made by the group of users. To do this, each user of the group is assigned a weight in view of the similarity of his rates with the rates of active user. Users whose rates are as close as possible to the active user ones, are combined into one group called neighbor. Taking into account the rates of these neighbors performed is the prediction of active user's rates and on this basis the system generates recommendation [15-20].

Item-based measures parameters of statistical models for users' rates. To construct these models different methods are used, the most common of which are the following: clustering, Bayesian networks, latent semantic model, Markov decision process, and others. The models are developed using data mining, machine learning algorithms to find patterns based on the training data [15-20].

Item-based approach gives more relevant results, as deeply analyze factors that explain the observed rates. Better than in user-based processed are sparse matrix, that contributes to the scalability of large data sets. But, at the same time, there is a possibility of loss useful information loss in connection with the reduction of models.

The main problem of collaborative filtering is the so-called problem of "cold start", i.e. the virtual absence of data on new sites or users [15-20]. New items or users are a big problem for recommender systems. A high entry threshold is necessary, without knowing anything about the user's interests, the recommendations are virtually useless. To some extent this problem can be solved by using a content-based approach, which is known to use attributes instead of rates. In addition to the "cold start" problem, we can also note...
the problem of the recommender system inability to distinguish similar items with different names. The same items having different names are called synonymous. Most modern systems are not able to discover the hidden connections between synonymous items. Interestingly can also be the problem of “white raven”. “White ravens” are users who have diverse tastes, their opinions do not always coincide with the majority of others. Accordingly, it is impossible to recommend anything. But it should be noted that the problems of these people come from real life, so it would not be entirely correct to call it a problem of recommender systems. The advantage of collaborative filtering is a theoretical accuracy.

In content-based filtering the profiles of users and items are created. User profiles may include demographic information or answers to a specific set of questions. Profiles of items can include the names of genres, actor names, artist names, etc., depending on the type of item. Items similar to those that the user has already used, are recommended to the user. Similarity is estimated on the basis of the items’ content. The main problems of these systems are the strong dependence on the subject area, as well as the fact that the usefulness of recommendations is limited. Advantage of this approach is that it can recommend to even unfamiliar users, thereby bringing them into service, it is possible to recommend the items that have not yet been evaluated by anyone. Disadvantage is a lower accuracy.

Hybrid systems, as the name implies, combines both filtrings, increasing the efficiency (and complexity) of recommender systems. Combining the results of the previous two types of filtering with a high probability can improve prediction accuracy. In addition, hybrid systems can partially solve the problem of the so-called “cold start” inherent in collaborative filtering. The hybrid approach first weighs the results according to the principles of the content filtering, and then, as soon as sufficient data on the analyzed user obtained, shifts the weights toward the collaborative filtering.

Knowledge-based recommender systems

In addition to the recommender systems, appeared at the dawn of the artificial intelligence development, i.e., content-based and collaborative, currently there are many systems that use in their work several different principles. Example of such systems may be a so-called “recommendations based on knowledge”. The data in them are not descriptive evaluations but deeper relationships. Knowledge-based, in some formal features, can be attributed to the content-based approach, but according to the existing classifications it is still referred to a separate class. In the knowledge-based recommendations considered are only the common characteristics of items, but deeper dependency are based on.

Information processed by “recommendations based on knowledge”, can be divided into: (a) rules (metrics) of similarity and (b) the items of interest. The system recommends items based on the user desires. User formulates his preferences in terms of the element properties, which, in turn, are presented in terms of rules (restrictions). A detailed review of decision-making mechanisms that can be used in filters of this kind are described in [21].

Hybrid recommender systems, in turn, can be divided into mixed-type, cascade and context.

**Mixed-type strategy**

The basis for a mixed-type hybrid model is a presentation of recommendations in a single integrated view. Data obtained as a result of other types of filtering, are assigned a certain weight. For example, an item that was the highest rated in the collaborative filtering, obtains 100 points, an item best estimated in the content-based filtering, obtains 50 points, etc.

**Cascade strategy**

According to the name, this method is characterized by cyclical way of building recommendations. The initial iteration is the algorithm, that is a gross filter, and all subsequent operations more and more refine results.

**Context strategy**

The main, characteristic of all existing recommender systems, mechanism of work is to develop recommendations based solely on the previously recorded ratings and user preferences. This mechanism has been used for a long time and therefore it is considered that it has developed all of its computing capacity, i.e. it is impossible to increase the effectiveness of recommendations using only this mechanism. There appears a need to use new data to make recommendations. Context can play a role of these new data.

Context is a data representing a characteristic of the situation in which the user is located and in which
the evaluation of the item occurs. In general, the context can be divided into 2 following types:
- context in which the user preferences are fixed;
- context in which the recommendation is formed;

Context can also be divided into the following types:
- time, location, type of user activity, weather, light and the like, i.e., physical context;
- presence of others and their roles, social context;
- specifications of the instrument, with the help of which access to the information is supported, i.e. device context;
- nature of the user, his experience, cognitive abilities, i.e. modal context.

Of course, all this makes sense only if the information listed above has a major impact on the selection of an item, carried out by the user.

Practical experience of the context recommendations application shows that the most valuable is the information about the current user, behavior of users in general, properties of recommended products and context of the current user interest [1-3].

Based on the experience obtained by many developers, we can conclude that the context application in recommendations is a promising direction.

The application of context can get rid of the problems typical to many recommender systems, especially collaborative ones: cold start (context allows to characterize a new user based on his psychological and national data, mood and professional affiliation), unusual user problems (taking into account individual characteristics makes it possible to personalize the recommendations in the best way), triviality of recommendations, "filter bubble" (the context allows us not to be limited by user’s last points of view). However, in the context systems, the problem of resource-intensive computations due to the large amount of data to be processed remains, and even increases.

Recommender systems in cardiology

Over the past few decades, number of medical data (test results, patient health records, treatment plans, and others) has reached enormous volumes. Consequently, the amount of information available for decision-making on patient treatment, increased significantly, but the problem is that this information is presented on various websites and resources and to gather it together is quite difficult. As a solution now proposed is the creation of personal electronic health cards (PEHC), which would be stored on a single resource, and would be available to both the patient and health care provider.

Moreover, recommender systems start being used in the medical field more often. These systems are used both by doctors and patients. The system allows doctors to speed up and simplify the process of diagnostics, the patient is able to get a preliminary consultation. Ricci et al. allocated the recommendation systems used in medicine, in a separate group, and called it "medical recommender system (MRS)" [6]. The MRS item is not confidential, scientifically proven, not tied to a particular patient medical information. MRS receives and processes data from PEHC of each particular user and on the basis of them builds the recommendations. Both the physician and patient get access to the MRS.

MRS are designed to provide the user with high quality relevant content. To achieve a high level of relevance a broader context should be considered. MRS takes into account the complex relationship between health concepts, decipher acronyms and interpret codes of medical classifications, adapts information to understand by an ordinary patient. Such systems are able to reduce the effect of information overload at the end user.

MRS determines the information needs of a particular user by analyzing PEHC records, user’s search queries or by tracing the history of user views. To obtain highly relevant recommendations many computing methods are used. First of all, information retrieval (IR).

Information retrieval is the process of searching unstructured information, which satisfies information needs [23,24].

Term "information retrieval" was first introduced by Kelvin Muersom in 1948 in his doctoral dissertation, published and used in the literature since 1950.

Information retrieval is a process of identifying a set of documents in all those that satisfy a predetermined search condition (query) or contain the necessary data. In most cases, the information retrieval includes wording, determination of information sources, retrieval of information from these sources, and final stage, acquaintance with information received and evaluation of the results.

The retrieval methods are the following: address, semantic, documentary and factual.
Classical task of information retrieval is a search for documents that satisfy the request, within a static document collection. But the list of tasks is constantly expanding and currently includes classification issues, filtering and clustering of documents, architecture design of search engines, information retrieval, querying, and others. [25-31]

For MRS, as well as for all recommender systems, advances in IR are essential. The use of IR allows obtaining relevant recommendations. The recommendation is based on PEHC which contain text documents, such as medical certificates, doctor’s orders, and others. These text documents serve as queries in IR. Capabilities of IR in query values matching can be applied to the problem of selection of the relevant recommendations in MRS.

It is believed that the collaborative filtering is not suitable for MRS because of the need to keep medical secret. You can challenge this statement, citing the fact that the user information is being processed by not a person but a machine. But to explain this to an ordinary user concerned about his data security is not easy. However, due to the fact that user data is processed during a single session, it is easier to hack a system based on collaborative filtering. Therefore, many researchers believe the content-based filtering is more appropriate for MRS. Content-based filtering can also partially solve the problem of "cold start".

Examples of working MRS are user-oriented web portals of medical information, offering the possibility of making a diagnosis based on symptoms. However, for unprofessionals, in these systems there is a risk of information overload. Moreover, it is difficult to provide relevant results in the system "when the user does not know exactly what he wants." Besides, in case when users of such web portals have an account, which displays PEHC, MRS gives much more accurate results [25-31].

Fernandez-Luque, Karlsen and Vognild [32] identified the MRS possibilities as an educational resource for people leading a healthy lifestyle. They proposed the use of so-called program-assistant which allows scanning medical scientific content provided in a variety of social networks.

Hu H, Elkus A, Kerschberg L. [33] described the system that allows extracting suitable for users with a specific disease information from Internet. The system gives the patient the ability to search relevant content. The authors emphasize that MRS in this case can be viewed as a "medical information storage". The paper also notes the capability of connection to social networks user profiles to improve the recommendations.

Rivero-Rodriguez et al. [34] developed a system that enriches the social network content (YouTube videos, etc.) with materials from medical sources, e.g. Medline Plus. Such an approach contributed to the improvement of such ontologies as a SNOMED-CT. However, the authors acknowledge the need for more accurate meta-data to improve the quality of recommendations.

Other systems are focused on the prevention of disease by sending recommendations to users on mobile gadgets. In practice, this means that people who suffer, for example, diabetes, or nicotine dependence, receive daily personalized advice on dieting and receive medication. Ghorai et al. [35] presented the MRS that helps smokers to quit this addiction. In this case, the system simulates the recommendations based on user behavior data.

In general, many MRS are primarily intended to provide the end user with respect to the recommendations on his health. Based on analysis of the patient’s history, the MRS sends to the PEHC user interface the data most appropriate for a particular patient, and of greatest interest to him [36-46]. The following data are most often in PEHC:

1. The detailed medical data about the user (for example, current treatment, further treatment plan, surgical reports, medical certificates, etc.)
2. The terms collected by PEHC based on the user’s search (for example, "the symptoms of myocardial infarction", "flu treatment", etc.)
3. The user behavior statistics (for example, visits to a certain web page, article ratings, etc.)

To obtain the most relevant recommendations MRS processes all of the above data, but paragraph 1 deserves special attention as it is based on information received from health care professionals.

When integrating MRS and PEHC the following requirements should be fulfilled:

1. The system should be able to interpret the following data:
   (A) imprecise terms (for example, "hepatitis" instead of "chronic viral hepatitis"),
   (B) colloquial expressions (for example, "period" instead of "menstruation"),
   (C) inaccurately written expression (e.g., "diaetes" instead of "diabetes").
2. The system should be able to understand professional terms used by doctors.
3. User’s data confidentiality must be guaranteed by the MRS developers and owners. Even PEHC administrators should not have access to data containing patient confidentiality.

Despite significant progress in the development of recommender systems, MRS had not yet become a part of everyday life. Many issues remain open. The MRS interface should be clear to both medical professionals and ordinary users of any age [36-46].

Among other things, a big problem is information security, especially preservation of medical confidentiality. The problem of integration of MRS and PEHC is still unsolved because of existing shortcomings in the field of security. Integration with PEHC is necessary because the information on patient available in PEHC can solve the problem of "cold start", i.e. absence of input data. Improving the quality of recommendations will help to motivate users to update data in PEHC. And, in turn, the actual PEHC data contribute to the relevance of recommendations. There also exists a problem consisting in the fact that the MRS has to choose among the PEHC entries just the entries responsible for the current state of patient’s health. Entries, which reflect the past diseases of the user, may no longer be relevant. MRS must be able to separate chronic diseases, e.g., diabetes, from diseases manifesting for a short period, e.g., seasonal colds.

An example of practical application of recommender systems in cardiology is a developed by Southampton University (UK) and the University of Islamabad iOs application [47]. The app is able to make a diagnosis and recommend appropriate treatment, diet and daily routine, by processing the data obtained from the biosensors located on the patient’s body. Application data is collected from millions of patients wearing biosensors. The collected data is processed by a hybrid recommender system. As a result, by comparing the obtained data with the known symptoms of cardiovascular disease, a diagnosis is made. The diagnosis is compared with the treatment algorithms existing in the base. After that, the system encourages the patient to undergo a certain course of treatment, a diet and other recommendations (Figure 1).

**Conclusion**

The concept of recommender systems is defined herein, the brief history of the recommender systems development is given. The main types of recommender systems and principles of their construction are presented. The article provides a detailed review of the recommender systems application in medical field, cardiology, in particular. Methods of recommender systems construction are given, advantages and disadvantages of the methods are provided. Efforts to improve applicable in cardiology recommender systems may be extended by improving the basic algorithm, the construction of other models of recommender systems, such as hybrid ones, processing larger arrays of additional data.

**Statement on ethical issues**

Research involving people and/or animals is in full compliance with current national and international ethical standards.

**Conflict of interest**

None declared.

**Author contributions**

The authors read the ICMJE criteria for authorship and approved the final manuscript.
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Introduction

Nowadays an analysis of the measuring ECG data processing is an important issue in the field of modern methods of data processing. The ECG data are usually collected non-invasively by ECG signal recording with the use of different types of electrodes placed on the human chest surface.

In practice, the required analysis of ECG data is provided with the help of specialized algorithmic means of primary and secondary data processing for making diagnostic decisions on the state of the cardiovascular system [1-4].

It is known [5-8] that the signal is inevitably affected by noises of the physiological and electrical origin when recorded with the use of the electrodes. To reduce the noises, taking into account the noise origin, various algorithmic tools of primary signal processing, in particular, noise filter algorithms, are currently being improved [5-8]. The noise effect leads to reducing the ECG signal accuracy [7].

The reliability and efficiency of the algorithmic means of the primary and secondary ECG signal processing largely depend on the used instrumentation of recording, namely, electrodes, which are responsible for formation of informative parameters of the signal against the background of noises [9]. The efficiency of the ECG signal processing analysis results, as well as the degree of complexity of the algorithmic processing tools designed to separate the informative parameters of a signal against the background of noises, depend on the quality of recording equipment. In case of a low quality of the ECG signal recording due to the characteristics of the electrodes themselves, some errors, which are associated with the formation of the ECG signal informative parameters and which in the process of noise filtering can be recognized as distortions introduced by filter algorithms, might occur. In doing so, as a consequence, algorithmic processing instruments, due to the distorted ECG signal segments at the classifier output, may produce erroneous diagnostic classification findings [10].

In view of the above, to improve the efficiency of processing the ECG data at present there is a necessity to jointly consider the measuring electrodes for the purpose of evaluation of their quality, which makes effects on the efficiency and reliability of the ECG signal...
processing analysis, in particular the means of noise filtering [11,12]. The necessity of such consideration consists in the following: first, characteristics of contact conductive agents have an influence on the accuracy of reproduction (formation) of the signal parameters, i.e. the minimization of losses of the obtained ECG signal informative segments in signal recording; second, it is required to increase accuracy of the ECG signal processing instrumentation against the background of affecting noises.

However, in [12] carried out is a comparative assessment of the characteristics of the wet electrodes for evaluating the accuracy of the formation of the ECG signal parameters formation during the long-term recording. In order to assess the quantitative indicators, characterizing the quality of the ECG signal recording instruments, measured are the values of electrical resistance in contact conducting agents (CCA) in different wet electrodes. The accuracy of the long-term ECG signal parameter formation in the process of recording has been evaluated with the use of the quantitative probability value. To calculate this value we have involved a highly experienced arrhythmia expert in our studies in order to properly count the number of correctly and erroneously recorded signal parameters referred to the total number of records. The recorded parameters are as follows: wave P, T and ECG signal complexes QRS. The result of the calculation of the above value shows that in all real long-term ECG signal records the most erroneous are the P wave records: the errors have been found for all leads there. The main error in the P wave formation has been detected in the form of splitting.

This article is a continuation of our study [12], where analyzed are the characteristics of wet electrodes and their collaborative evaluation of the accuracy of the signal parameters formation. In the present paper we analyze the effect of electric resistance in the contact conductive agents of different wet electrodes on the accuracy of the P wave formation in an ECG signal through correlation relationships.

Aims

The aim of this study is to evaluate the correlation relationships between the values of electric resistance in the conductive contact agents of different wet electrodes and probability values characterizing the accuracy of the ECG signal P wave formation.

Materials and methods

The material for the study are the measured values of electric resistance of CCA, which are a widely used in models of wet electrode for ECG signal recording, namely: H92SG, H99SG, MSGLT-05MGRT, M2202A, and the calculated probability values characterizing the accuracy of the P wave formation during signal recording [12]. The values of electrical resistance for the confidence probability of Student distribution quantile $P=0.95$ at $(n-1) t_{\alpha}=0.05$ are presented in Table 1 herein. The probability values of true recording for different electrodes are shown in Table 2 given herein. Table 2 shows the probability value without leads aVL, II. It is feasible to present the obtained data in order to evaluate the accuracy of the P wave formation in 10 electrodes of each trade name during long-term recording, similar to the case described in [12].

Table 1

<table>
<thead>
<tr>
<th>№</th>
<th>Electrode type</th>
<th>Measurement results for confidence probability $P=0.95$ ($\alpha=0.05 \rightarrow t_{\alpha}=2.26; n-1$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H92SG</td>
<td>($79.348\pm0.313$)</td>
</tr>
<tr>
<td>2</td>
<td>H99SG</td>
<td>($174.46\pm0.452$)</td>
</tr>
<tr>
<td>3</td>
<td>MSGLT-05MGRT</td>
<td>($30.623\pm0.443$)</td>
</tr>
<tr>
<td>4</td>
<td>M2202A</td>
<td>($21.523\pm0.359$)</td>
</tr>
</tbody>
</table>

Our evaluation of the correlation relationship between two variables for better visualization is analyzed by scatter plotting. Scatter plotting is a statistical method that shows the distribution of two variables: a dependent variable and its predictor [13]. The dependent variable is selected as a result of a direct measurement of electrical resistance in the electrode CCA, and for the predictor we use in our case an indirect measurement result, i.e. the probability value. The predictor is a variable in the context of the present study. The plausibility of the obtained scatter plot is checked using the trend line with specified values of the confidence probability intervals. To construct the confidence probability intervals, selected is probability value $P=0.95$ for significance level $\alpha=0.05$, respectively. The scatter plot is analyzed with the use of the STATISTICA 10.0 software (StatSoft) [14].

Results

The results of the evaluation of the correlation relationship of the analyzed variables with the use of scatter plots are shown in Figures 1-4 herein. The calculated correlation coefficient is indicated in Table 3 herein.
Table 2
Probability of true recording in a lead

<table>
<thead>
<tr>
<th>№</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>V5</th>
<th>V6</th>
<th>I</th>
<th>III</th>
<th>aVR</th>
<th>aVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT(P)</td>
<td>*</td>
<td>0.65</td>
<td>0.64</td>
<td>0.75</td>
<td>0.53</td>
<td>0.62</td>
<td>0.70</td>
<td>0.68</td>
<td>0.63</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>**</td>
<td>0.80</td>
<td>0.70</td>
<td>0.85</td>
<td>0.86</td>
<td>0.89</td>
<td>0.85</td>
<td>0.54</td>
<td>0.78</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>***</td>
<td>0.95</td>
<td>0.94</td>
<td>0.97</td>
<td>0.96</td>
<td>0.94</td>
<td>0.95</td>
<td>0.96</td>
<td>0.92</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>****</td>
<td>0.70</td>
<td>0.74</td>
<td>0.88</td>
<td>0.89</td>
<td>0.79</td>
<td>0.74</td>
<td>0.54</td>
<td>0.69</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Note: Results of probabilities calculation for the electrodes are indicated

Table 3
Coefficient of correlation between values from electrodes

<table>
<thead>
<tr>
<th>№</th>
<th>Electrode type</th>
<th>Coefficient of correlation between values R:P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H92SG</td>
<td>0.4809</td>
</tr>
<tr>
<td>2</td>
<td>H99SG</td>
<td>0.3526</td>
</tr>
<tr>
<td>3</td>
<td>MSGLT-05MGRT</td>
<td>0.3280</td>
</tr>
<tr>
<td>4</td>
<td>M2202A</td>
<td>- 0.0343</td>
</tr>
</tbody>
</table>

The obtained results given in Table 3 and illustrated by Figures 1–3 show that the correlation relationship exists between the values of electric resistance and the probability value. The correlation relationship between the probability value for H92SG is $r = 0.4809$, for H99SG $r = 0.3526$, and for MSGLT-05MGRT $r = 0.3280$, respectively. Our analysis of scatter plots in Figures 1-3 shows that apparent outliers have not been found, and the observation points are within the confidence interval. However, in each of the H92SG, H99SG and MSGLT-05MGRT electrodes, two observations go beyond the confidence limits that indicates the absence of outliers.

However, the correlation analysis of the dependence for the M2202A electrode gives us a negative value of this ratio, namely $r = - 0.0343$. The analysis of the scatter plots for the given electrode shows that there are four outliers beyond the confidence limits of the probability interval $P = 0.95$.

We should note that in [12] the H92SG, H99SG, MSGLT-05MGRT and M2202A electrodes differed from each other in the state of their contact conductive agents, namely, liquid and solid. The M2202A electrode, during the long-term evaluation of its CCA, demonstrated changes in its reference characteristics due to an error, which occurred because of spreading of liquid CCA beyond the specified area of the electrode measuring cell. The calculated error in [12] for the M2202A electrode shows that there are outliers beyond the confidence limits of probability interval $P = 0.95$ and a negative correlation between the variables. The lower the outliers on a scatter plot, the more variables are grouped around the trend lines, and, accordingly, the greater is the correlation value, that is different from zero, between the studied variables.

Thus, systematizing the results obtained above, we can conclude that the accuracy of the ECG signal parameters formation during long-term signal recording is influenced by liquid state of CCA in electrodes. As a consequence, electrodes with solid CCA have the most appropriate characteristics for use in long-term monitoring of the ECG signal parameters. This conclusion can be supported by the results of study [12] and the evaluation of the relationship between the electrodes characteristics with
the use of the scatter plots. The scatter plots allow us to visually assess the strength of the correlation between the studied variables and outliers beyond the confidence limits of the probability interval that makes it possible to identify the effect produced by the electrodes characteristics on the accuracy of the formation of electrical cardiac signal parameters for each electrode in the scope of the considered trademarks.

Conclusions
Thus, the results of our analysis of the effects produced by the respective electrode characteristics on the accuracy of the formation of the ECG signal parameters are presented herein. In electrodes with solid CCA the accuracy level of the formation of the ECG signal parameters is significantly higher as compared with the electrodes containing liquid CCA.

Funding
The research is supported by the Russian Federation Government (Grant 08-08).

Statement on ethical issues
Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest
None declared.

Author contributions
The authors read the ICMJE criteria for authorship and approved the final manuscript.

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11. Altaj EA, Kremlev AS. Formirovanie kompleksnogo podhoda dlya analiza obrabotki izmeritel’nogo


Rose Angina Score can really estimate myocardial perfusion scan results in both diabetic and non-diabetic patients?

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Aims
Cardiovascular diseases are among the most important causes of mortality and morbidity worldwide. There are different risk factors explained for cardiovascular diseases and diabetes mellitus (DM) is notable among them. There are different modalities for diagnosis and risk assessment of cardiovascular diseases such as myocardial perfusion imaging (MPI) but considering high price and low accessibility of this modality we decided to assess any possible association between MPI findings and Rose angina score (RAS) in both diabetic and non-diabetic patients.

Materials and methods
In this descriptive-analytic study we enrolled 585 diabetic and non-diabetic patients with angina pectoris referred to nuclear medicine department of Shahid Sadoughi hospital, Yazd, Iran for MPI. Patients demographic information along with MPI results and Rose angina questionnaire were obtained. Data were finally analyzed using SPSS ver.21 software using appropriate statistical tests.

Results
In this study, there were 294 diabetic and 291 non diabetic patients enrolled. 61.9% of non-diabetic patients had normal MPI results but this amount was only 38.8% among diabetic patients. Our study population did not differ based on age, gender and Rose angina score between diabetic and non-diabetic patients. Our results indicate that there is a statistically significant association between RAS and MPI findings in both diabetic (P-value=0.001) and non-diabetic (P-value=0.001) patients.

Conclusion
In present study we found a significant association between simple RAS questionnaire and MPI findings. We do not deny high accuracy and diagnostic value of MPI but we want to focus on clinical judgement of physicians prior to imaging modalities. We believe that in many cases, with a good clinical assessment such as RAS, many unnecessary and expensive modalities can be avoided.

Keywords
Rose angina score, Rose angina questionnaire, Diabetes mellitus, Myocardial perfusion scan, Cardiovascular disease, Coronary artery disease, Ischemia

Imprint

Introduction
Cardiovascular diseases are one of the most common causes of death in almost whole world. They devote more than 30% of mortality in developed countries. Cardiovascular diseases cause mortality, morbidity and complications which put a heavy economic burden on society (1, 2).

Different factors are said to be involved in development of coronary artery diseases such as gender, age and genetics which are not adjustable. There are some other factors that can be controlled or even eliminated such as diabetes mellitus (DM), hypertension (HTN), obesity, smoking, hyperlipidemia (HLP), psychological tension and etc. (3-5).

Myocardial perfusion imaging (MPI) is one of non-invasive diagnostic modalities in field of cardiovascular imaging which can accurately detect ischemia in myocardium(6). In many studies it is said that MPI can avoid unnecessary economical payments for risk assessment of cardiovascular events(7). Accuracy of MPI has been reported differently in different investigations (8, 9).

During 1993 and 2001 stress cardiovascular imaging has increased to 3 fold as before. MPI has been
used 3 times more than stress echocardiography and 2 times more than exercise stress tests since 1996. Considering rapid development and application of this modality some insufficiencies have been also reported for this modality. In several clinical conditions MPI is the most common used modality for evaluating myocardial perfusion status(10, 11).

Although different diagnostic modalities such as exercise stress test, MPI, angiography are really valuable in diagnosis of coronary artery disease (CAD), but the chance to use them is not prepare and equal for all people. In some regions and societies it seems that it is necessary to know importance and capabilities of other non-invasive, cheap, rapid and accessible modalities too(12).

For the first time Dr. Rose innovated a questionnaire to diagnose CAD and later was applied by other researchers in different regions as a very cheap modality for diagnosis of CAD. This questionnaire possess a sensitivity of 78 to 81 % and specificity of 94 to 97% compared to clinical judgement(13-15).

Nowadays DM is known as a comorbidity which is associated with an elevated risk of cardiovascular event and can lead to early death or disability followed by myocardial ischemia. Risk of cardiovascular events increase 2 to 4 folds in diabetic patients compared to non-diabetics. Diabetic patients have a more complicated cardiovascular disease at the time of primary diagnosis. MPI is a good screening method for coronary artery disease in diabetic patients(16, 17).

Considering important role of MPI in diagnosis of CAD and also high expenses and low accessibility for a great percentage of patients along with accessibility and simplicity of Rose angina questionnaire, in this study we decided to investigate possible association between Rose angina score (RAS) and MPI results in diabetic and non-diabetic patients. We think that this study can help to clarify diagnostic importance of RAS in comparison to MPI.

Materials and methods

This study is a descriptive-analytic study performed on 585 diabetic and non-diabetic patients with angina pectoris referred to department of nuclear medicine of Shahid Sadoughi hospital, Yazd, Iran for myocardial perfusion scan during 2019. All patients signed an informed consent to let us use their medical information for research purpose. This study was designed and performed based on Helsinki declaration and is registered in committee of research ethics of Shahid Sadoughi university of medical sciences, Yazd, Iran with IR.SSU.MEDICINE.REC.1398.260 approval ID.

We included 300 diabetic and 300 non diabetic patients with angina pectoris that were referred to nuclear medicine department for MPI. 15 patients that were not available or their medical folder was corrupted were excluded and finally 585 complete folders were elected for further analysis.

MPI were done via Gamma camera device with 128 by 128 matrix in both rest and stress condition for all patients. All patients underwent physical stress and 20 to 25 milli curvy Tc99m-MIBI was used for all images. MPI results were reported and categorized in a 5-point scale as normal, mild ischemia, moderate ischemia, severe ischemia and no perfusion.

A Rose angina score questionnaire was also used for all patients in which patients are categorized in 3 categories based on assessed risk as: score below 6 as low risk, score between 6 and 11 as moderate risk and score above 11 as severe risk. Patients angina pectoris is also categorized in 3 degrees as: 1) grade 2 definite angina (severe) in which patients feel pain while walking on even land rather than inclined ground. 2) grade 1 definite angina (moderate) in which patients answer all questions positive. 3) possible angina (mild) in which not all answers are positive but angina pain occurs while walking with hurry or on inclined ground.

All patient's demographic information including gender, age, comorbidities, Rose angina score and ischemia detected in MPI were recorded in a questionnaire and finally all data were analyzed using SPSS ver.21 software using appropriate statistical tests such as Chi-square, independent T test or paired T test. In all tests a P-value<0.05 was considered to be statistically significant.

Results

This is a descriptive-analytic study performed in 2019 to assess the relationship between Rose angina score and MPI results in diabetic and non-diabetic patients. Among 585 enrolled patients, 294 (50.3%) of them were diabetic and 291 of them (49.7%) were not diabetic. 399 (68.2%) patients were diagnosed with HTN and 75 (12.8%) patients remarked a history of prior myocardial infarction.

In our study population mean patients age was 58.33±10.8 and ranged between 24 and 87. Based on RAS, 201 (34.4%) of them had probable angina, 135 patients (23.1%) had grade 1 definite angina and 249...
### Table 1
Descriptive statistics of patients based on age and gender

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
<th>Mean age</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>198 (67.3%)</td>
<td>96 (32.7%)</td>
<td>58.89</td>
<td>294 (100%)</td>
<td></td>
</tr>
<tr>
<td>Non-diabetic</td>
<td>177 (60.8%)</td>
<td>114 (39.2%)</td>
<td>57.76</td>
<td>291 (100%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>375 (64.1%)</td>
<td>210 (35.9%)</td>
<td>58.33±10.8</td>
<td>585 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

Gender = 0.1, Age = 0.2

### Table 2
Association between DM and HTN. HTN is significantly more in diabetic patients (P-value=0.001)

<table>
<thead>
<tr>
<th>History of HTN</th>
<th>No HTN</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>237 (80.6%)</td>
<td>57 (19.4%)</td>
<td>294 (100%)</td>
</tr>
<tr>
<td>Non-diabetic</td>
<td>162 (55.7%)</td>
<td>129 (44.3%)</td>
<td>291 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>399 (68.2%)</td>
<td>186 (31.8%)</td>
<td>585 (100%)</td>
</tr>
</tbody>
</table>

### Table 3
Association between DM and history of ischemia. There is a statistically significant association between DM and history of ischemia (P-value=0.04)

<table>
<thead>
<tr>
<th>History of ischemia</th>
<th>No HTN</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>45 (15.3%)</td>
<td>249 (84.7%)</td>
<td>294 (100%)</td>
</tr>
<tr>
<td>Non-diabetic</td>
<td>30 (10.3%)</td>
<td>261 (89.7%)</td>
<td>291 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>75 (12.8%)</td>
<td>510 (87.2%)</td>
<td>585 (100%)</td>
</tr>
</tbody>
</table>

### Table 4
Descriptive results associated with frequency of different MPI abnormalities in both diabetic and non-diabetic patients

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Mild ischemia</th>
<th>Moderate ischemia</th>
<th>Severe ischemia</th>
<th>No perfusion</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>114 (38.8%)</td>
<td>99 (33.7%)</td>
<td>30 (10.2%)</td>
<td>36 (12.2%)</td>
<td>15 (5.1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-diabetic</td>
<td>183 (62.9%)</td>
<td>45 (15.5%)</td>
<td>24 (8.2%)</td>
<td>24 (8.2%)</td>
<td>15 (5.2%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>297 (50.8%)</td>
<td>144 (24.6%)</td>
<td>54 (9.2%)</td>
<td>60 (10.3%)</td>
<td>30 (5.1%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5
There is no statistically significant association between RAS and DM (P-value=0.93)

<table>
<thead>
<tr>
<th></th>
<th>Mild (probable angina)</th>
<th>Moderate (grade 1 definite angina)</th>
<th>Severe (grade 2 definite angina)</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>102 (34.7%)</td>
<td>69 (23.5%)</td>
<td>123 (41.8%)</td>
<td>294 (100%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Non-diabetic</td>
<td>99 (34%)</td>
<td>66 (22.7%)</td>
<td>126 (43.3%)</td>
<td>291 (100%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>201 (34.4%)</td>
<td>135 (23.1%)</td>
<td>249 (42.6%)</td>
<td>585 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 6
Association between RAS and MPI results in diabetic patients. There is a significant association between RAS and MPI abnormalities in diabetic patients (P-value=0.001)

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>66 (57.9%)</td>
<td>24 (21.1%)</td>
<td>24 (21.1%)</td>
<td>114 (100%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mild ischemia</td>
<td>36 (36.4%)</td>
<td>33 (33.3%)</td>
<td>30 (30.3%)</td>
<td>99 (100%)</td>
<td></td>
</tr>
<tr>
<td>Moderate ischemia</td>
<td>0 (0%)</td>
<td>12 (40%)</td>
<td>18 (60%)</td>
<td>30 (100%)</td>
<td></td>
</tr>
<tr>
<td>Severe ischemia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>36 (100%)</td>
<td>36 (100%)</td>
<td></td>
</tr>
<tr>
<td>No perfusion</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>15 (100%)</td>
<td>15 (100%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>102 (34.7%)</td>
<td>69 (23.5%)</td>
<td>123 (41.8%)</td>
<td>294 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 7
Statistically significant association between RAS and abnormal MPI findings in non-diabetic patients (P-value=0.001)

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>90 (49.2%)</td>
<td>54 (29.5%)</td>
<td>39 (21.3%)</td>
<td>183 (100%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mild ischemia</td>
<td>9 (20%)</td>
<td>12 (26.7%)</td>
<td>24 (53.3%)</td>
<td>45 (100%)</td>
<td></td>
</tr>
<tr>
<td>Moderate ischemia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>24 (100%)</td>
<td>24 (100%)</td>
<td></td>
</tr>
<tr>
<td>Severe ischemia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>24 (100%)</td>
<td>24 (100%)</td>
<td></td>
</tr>
<tr>
<td>No perfusion</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>15 (100%)</td>
<td>15 (100%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>99 (34%)</td>
<td>66 (22.7%)</td>
<td>126 (43.3%)</td>
<td>291 (100%)</td>
<td></td>
</tr>
</tbody>
</table>
patients (42.6%) had grade 2 definite angina. Considering MPI results, 297 patients had normal results, 144 (24.6%), 54 (9.2%), 60 (10.3%) and 30 patients (5.1%) had mild ischemia, moderate ischemia, severe ischemia and no perfusion respectively.

In our study, among diabetic patients 198 (67.3%) of them were women and 96 (32.7%) of them were men. Mean diabetic patients age was 58.89 years. There were 177 (60.8%) women and 114 (39.2%) men within non diabetic patients. Mean age of non-diabetic patients was 57.76 years. Based on performed analysis there was no significant difference between diabetic and non-diabetic patients based on gender (P-value=0.1) and age (P-value=0.2). table No.1 below shows descriptive statistics associated with patient's gender and age.

In this study 80.6% of diabetic patients had HTN and 55.7% of non-diabetic patients had HTN. With a P-value of 0.001 it means that diabetic patients had a significantly higher rate of HTN. table No.2 shows the association between DM and HTN in our study.

Our results show that there is also a significant association between history of ischemia and diabetes. Association between DM and history of ischemia is summed up in table No.3.

Chi-square analysis results indicate that there is a statistically significant difference between diabetic and non-diabetic patients in terms of abnormalities of MPI. As also seen in table No.4, 62.9% of non-diabetic patients had normal MPI and only 38.8% of diabetic patients had normal MPI results.

As seen in table No.5 below our results indicate that there is no statistically significant difference between diabetic and non-diabetic patients based on their RAS (P-value=0.93).

Remembering main goal of our research which was to evaluate any possible association between RAS and MPI abnormality, we separately analyzed our data for this association in both diabetic and non-diabetic patients. As seen in table No.6, there is a significant association between RAS and MPI abnormality in diabetic patients.

Our findings show the same significant association between RAS and MPI findings in non-diabetic patients too (P-value=0.001). The results are summed up in table No.7.

Discussion

There are 200 million people living with diabetes around the world. Risk of cardiovascular involvement in diabetic patients in 2 to 4 times more than non-diabetic population (18, 19). In European and American guidelines DM is considered equal to cardiovascular involvement. Prevalence of coronary artery diseases among diabetic patients has been reported to be 43 to 53% regardless of gender (19). Considering high quality and value of MPI along with lack of accessibility for all patients and high expenses, in this study we decided to see if simple RAS questionnaire can be associated with MPI findings in diabetic and non-diabetic patients or not.

In this study we found that there is a statistically significant association between MPI findings and RAS in both diabetic and non-diabetic patients. There was a significant correlation between HTN and history of ischemia with DM. our both diabetic and non-diabetic populations were not different based on age, gender or RAS.

In a study performed in Iran by Habibian et al., regression analysis results showed a positive and powerful correlation between RAS and HTN, DM, smoking and gender (20). Other similar studies also showed the same results (21). Our study was a bit different because they investigated general population but we enrolled susceptible patients with angina pectoris which were going to undergo MPI.

A large population of 6498 patients above 35 years old were studied by Sadeghi et al. and researchers reported that prevalence of coronary artery disease was 37.5% in women and 22.2% in men based on RAS questionnaire. They found that prevalence of coronary artery disease increases by age. They also reported that documented myocardial infarction based on electrocardiogram is recorded higher in men compared to women but the prevalence based on RAS was higher in women in all age groups (22).

Poudel et al. investigated 100 patients with chest pain referred to emergency department. They found that RAS questionnaire possess 63.8% true positive and 33.3 true negative for diagnosis of MI. true positive MI cases after cardiology consult was reported to be 71.6% which indicates reliability of Rose questionnaire (23).

In a comprehensive study performed by Hui et al. on 1957 patients with coronary artery disease, 619 of them were diabetic. They found that there is no significant difference between diabetic and non-diabetic patients based on their RAS questionnaire which is in accordance with our results (24).

Another similar study performed by Rahman et al. showed that history of HTN and myocardial ischemia in diabetic patient is significantly higher in compar-
ison to non-diabetic patients but similar to present study, RAS was not significantly different between diab
tic and non-diabetic patients(14).

It seems that performing an appropriate screening
before MPI can reduce number of unnecessary scans. 
This risk assessment method seems to be useful in diab
tic patients with higher risk of silent ischemia too.

Park et al. revealed that risk RAS questionnaire is 
similar to coronary CT angiography in risk assessment
of coronary artery diseases. Their study also indicated 
that DM, HTN, family history and history of previous 
ischemia is significantly correlated with severity isch
emia (25) ar.

Considering all mentioned above findings, it seems 
that although MPI is a really powerful and acceptable
modality but it still cannot be completely replaced 
with physical examination, history taking and clini
cal judgement of physicians. By this study we did not 
want to deny usefulness and high value of MPI but we 
wanted to attract attention and focus on clinical judg
ment. We believe that by having appropriate medical
knowledge and a good clinical insight, physicians can 
get even better results out of paraclinical modalities.

Conclusion

Our results showed that RAS is associated with se
verity of perfusion defect detected via MPI. We con
clude that in patients with high risk angina pectoris
such as diabetic patients, hypertensive patients and
patients with history of previous ischemia, by means 
of appropriate use of RAS, it is possible to avoid un
necessary MPI.

We do not claim that RAS is a more powerful tool
for assessment of coronary artery disease compared to
MPI, but we think that a good clinical judgement and
insight can avoid unnecessary expenses and can lead to 
a better application of imaging modalities.

Statement on ethical issues
Research involving people and/or animals is in full 
compliance with current national and international 
ethical standards.

Conflict of interest
None declared.

Author contributions
The authors read the ICMJE criteria for authorship and 
approved the final manuscript.

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stress SPECT myocardial perfusion imaging as an ini
tial diagnostic strategy in stable patients with chest
pain and suspected CAD: cost analysis. Journal of nu
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Effects produced by automated plasmapheresis on morphofunctional data on cardiovascular system performance in ischemic heart disease patients

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Abstract

We have performed the study of the effects made by the automated plasmapheresis application on ischemic heart disease clinical manifestations, echocardiographic indices and heart rate variability in patients with exertional angina III-IV functional class. It has been found that the applied plasmapheresis method is capable to reduce the severity of the disease clinical manifestations and improve the echocardiographic characteristics of the heart, in particular, reduce the level of end-diastolic volume, and increase ejection fraction. The clinical effect is already apparent at the early stages of the treatment and remains unchanged even after 6 months thereof. Also revealed has been the normalization of heart rate variability, indicating a decreased activity of the sympathetic nervous system. It is concluded that the plasmapheresis method can be successfully used in practice by a wide range of hospitals, where patients with ischemic heart disease are monitored, including the ambulatory conditions.

Keywords

Exertional angina, Plasmapheresis, Echocardiography, Heart rate variability, Holter monitoring

Introduction

It is well known that so far CVD and first of all ischemic heart disease (IHD) remain the main causes of mortality of population in the Russian Federation [2]. In addition to the existing medication and a wide application of invasive methods for IHD treatment, for last decades some methods of alternative treatments have being introduced into clinical practice for this sort of patients that includes the efferent therapy techniques [1, 3-5]. In this connection, we should mention that the problem of an adequate extracorporeal assistance retains its topicality in the context of the complex treatment of ischemic heart disease because there are a number of factors as listed below: a high occurrence rate of this pathology, the disease severity, some predictable complications, an increasing cohort of younger patients and resistance to medication due to available metabolic disorders [2, 4, 12].

One of the most pathogenetically substantiated and, therefore, promising approaches to the treatment of the patients with ischemic heart disease (IHD), in particular exertional angina, is the use of plasmapheresis (PP). However, at the same time, there are only some fragmented single reports on capabilities of this approach, and there are no data on factors responsible for effects and determining efficacy of the plasmapheresis method application; no works are available which relate to justification of the use of different modes of PP application in CHF therapy.

Aims

The aim is to study some effects produced by the automated plasmapheresis (PP) technique on clinical signs in ischemic heart disease patients and on instrumental laboratory data on the cardiovascular system performance

Materials and methods

The study was carried out on the basis of the Russian Institution for Medical Problems of the North Region of the North Division of the Russian Academy of Med-
ical Sciences and the Clinical Transfusiology Chair at the Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov – First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University).

For the purpose of investigation of the PP efficacy, an examination and treatment of 130 IHD patients (exertional angina pectoris functional class III-IV) have been performed. The recorded disease history of the patients has been ranged from 2 till 22 years. The main test group covered 65 males and 33 females, aged from 40 to 75, with an average age 56.8±15.1 years.

32 patients (in the reference group) have completed the standard medication treatment without PP applications (medication including nitrates, beta-blockers, antiplatelets, angiotensin converting enzyme inhibitors and some other medical drugs).

The main test group has covered patients (n=98) who have undergone plasmapheresis (PP) in addition to the standard treatment.

Plasmapheresis was carried out using the Haemonetics device. Before performing the plasmapheresis treatment, a patient’s state was assessed, laboratory tests were performed (complete blood count, biochemical studies, coagulogram), a vascular access was selected, a volume of extracted plasma was identified and an amount and the character of plasma-substituting solutions, which were expected to use, were evaluated. When selecting the treatment procedure options, we took into account the volume of plasma removed per treatment session and per course, and the characteristics of substituting solutions (crystalloid, colloid). The total volume of plasma, which was removed in a treatment session, ranged from 0.3 to 1.5 l, and the course included 3-4 treatment sessions. During a single treatment procedure, 25-50% and more of the circulating plasma volume was removed, depending on the patient’s actual state, his/her clinical symptoms, comorbidity, the patient’s age, the presence of cardiac arrhythmias and the level of electrolytes. The removed plasma was replaced with crystalloid (0.9% sodium chloride solution, Ringer’s solution) and colloid (rheopolyglukin) or protein (5% albumin) solutions.

During the comprehensive examination of all above mentioned patients, the following has been carefully analyzed: their medical history records, their complaints and disease manifestations; performed were the relevant instrumental laboratory tests and examinations. The clinical efficacy of the treatment has been evaluated according to the following parameters:
- the number of anginal chest pain episodes per day (NACPED);
- the duration of a pain episode (DPE);
- a total of nitroglycerin tablets taken by the patient in a day (NTT).

Carried out was an instrumental examination, including roentgenoscopy of the lungs and the mediastinum using X-ray machine Siemens Axiom R 200; for each individual recorded were an ECG using GE MAK 5000 device and an echocardiogram with GE Vivid 4. When assessing morphofunctional cardiac parameters, measured were an end-systolic left ventricular volume (ESV), an end-diastolic left ventricular volume (EDV), stroke volume (SV), ejection fraction (EF), left atrial volume (LA), hemodynamic parameters Ve and Va, Ve/Va ratio and VIR.

The 24 hour-Holter monitoring has been completed in all patients followed by Heart Rate Variability (HRV) analysis, including both the time-related and power spectral analysis, since the Holter monitoring is the most informative, wide-spread, technique to assess the tonus of the autonomic nervous system. In doing so, the time and frequency domain analysis has been applied. For the purpose of this study, we have used the complete set of the following parameters: the R-R interval data (standard deviation, SDNN, µs.), the standard deviation of all mean 5-minute normal sinus intervals over 24 hours, SDANN, µs., and square root of the mean of the sum of the squares of differences between adjacent normal R-R intervals, r-MSSD. In this case, the SDNN index reflects the general tonus of the autonomous system activity; the parasympathetic tonus is described by the r-MSSD index, and the SDANN parameter is a fingerprint of the sympathetic system activity.

For the purpose of the heart rate variability analysis, we have utilized the complete sets of the parameters as listed below: the spectral power of High Frequency waves (HF), the respective Low Frequency (LF) and Very Low Frequency (VLF) components (the frequency ranges 0,15-0,35 Hz, 0,05-0,15 Hz and 0,004-0,05 Hz, respectively); we have also estimated an LF/HF ratio, too. It is considered that HF is an indication of the tonus modulated by the parasympathetic activity of ANS, while the LF component, the LF/HF ratio and the VLF component are distinguishing features of the sympathetic nervous system activity.
The data have been collected and their profiles have been compared upon the completion of 1, 7, 30 and 180 days of the treatment.

The obtained statistics parameters have been processed with use of the Statistica 8.0 software package. The applied methods of the descriptive statistics analytics have employed estimation of the set’s mean value (M) and the standard deviation. The Chi-square test (known as χ²-test) with the Yates continuity correction has been applied by us in order to establish statistically significant relationships between categorical qualitative binary variables between the compared paired groups. The nonparametric Mann–Whitney U test has been conducted in order to compare the differences that come from the quantitative indicators in different groups.

The critical level to indicate that the null hypothesis is true has been assumed to be 0.05.

Results and discussion

The completed designed studies have shown that plasmapheresis, included into the therapy scope, administered to the patients with exertional angina functional class III-IV, has made a noticeable effect on the majority of the recorded clinical and instrumental laboratory data. So, the changes in the clinical manifestations in these patients have been detected already within the first 7 days from the beginning of the plasmapheresis use, and the changed parameters have been maintained within the 1- to 6-month period: a number of the parameters have demonstrated significant changes as compared with the respective parameter values recorded in the reference group. Specifically, we have reported an improved condition pattern in the above category of the patients: the number of angina-attack-associated chest pain episodes has been decreased by 24-43%; recorded has been a reduction in the chest pain episode duration by 34-48 %, and the use of the nitroglycerine tablets has been reduced up to 32-41 % (see Table 1 herein).

Improved echocardiographic characteristics in the patients with exertional angina functional class III-IV, who have completed plasmapheresis procedures, have been reported within the 1- to 6-month period: there have been significant changes in the parameters detected, as compared with those in the reference group, as follows: the EDV value has been found to be higher by 2-6 %, the ESV parameter has been detected by 6-14% higher, and the ejection fraction value has been increased by 6-7% (see Table 2 herein). In general, the patients in the main test group have demonstrated favorable changes in the parameters, that has indicated the normalization both of the diastolic and systolic function of the heart.

### Table 1

<table>
<thead>
<tr>
<th>Data</th>
<th>Reference group (n=32)</th>
<th>Main test group (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7 days</td>
<td>1 month</td>
</tr>
<tr>
<td>NAPCPE</td>
<td>2,72±0,34</td>
<td>3,61±0,51</td>
</tr>
<tr>
<td>DPE, min.</td>
<td>5,72±0,74</td>
<td>4,78±0,68</td>
</tr>
<tr>
<td>NTT/day</td>
<td>1,67±0,34</td>
<td>1,79±0,40</td>
</tr>
</tbody>
</table>

Note: * - variances are plausible (at p<0,05) referred to the respective level in the reference group

### Table 2

<table>
<thead>
<tr>
<th>Data</th>
<th>Reference group (n=32)</th>
<th>Main test group (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7 days</td>
<td>1 month</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>61,2±1,6</td>
<td>59,4±3,6</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>142,2±8,3</td>
<td>138,5±7,2</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>81,0±8,7</td>
<td>79,1±7,2</td>
</tr>
<tr>
<td>EF (%)</td>
<td>57,0±4,7</td>
<td>57,1±3,7</td>
</tr>
<tr>
<td>LA (ml)</td>
<td>41,5±3,1</td>
<td>40,5±3,1</td>
</tr>
<tr>
<td>Ve (m/s)</td>
<td>0,513±0,16</td>
<td>0,532±0,24</td>
</tr>
<tr>
<td>Va (m/s)</td>
<td>0,502±0,27</td>
<td>0,493±0,18</td>
</tr>
<tr>
<td>Ve/Va</td>
<td>0,981±0,16</td>
<td>1,091±0,08</td>
</tr>
<tr>
<td>VIR (ms)</td>
<td>94,4±4,1</td>
<td>93,4±3,6</td>
</tr>
</tbody>
</table>

Note: * - variances are plausible (at p<0,05) referred to the respective level in the reference group.
Upon expiration of 6 months of the studies, the dynamics of the changes has been found to be slightly less pronounced, but however in this period of time the majority of the analyzed parameters in the patients of the main test group has shown positive dynamics of the changes: we have observed a decrease in the ESV and EDV values and an increase in the Ve and Ve/Va parameters.

Our HRV analysis of the Holter monitoring data in patients with exertional angina functional class III-IV has shown that the applied approaches to the treatment in the patients both of the reference group and main test group have produced some effects on the HRV data: that has induced an increase in the HRV HF component (RMSSD, HF), a decrease in the LF/HF index, a reduction in the number of ST depression and elevation episodes and the VE and SVE events a day (see Table 3 herein). At the same time, we should note when comparing the efficacy of both treatment versions, more favorable outcomes have been found in the main test group, where the combined therapy including PP has been used. In case with the PP-integrated treatment, we have detected differences in the data characterizing the efficacy of the treatment in all periods of our studies: the parameters of the Holter monitoring, which reflect the heart rate variability, the state of the electrical stability of the heart and the occurrence rate of ventricular and supraventricular extrasystole episodes have demonstrated better dynamics in those patients with exertional angina functional class III-IV, who have completed the treatment with PP included. The positive differences have been detected in this sort of patients already after day 7 from the beginning of the therapy, and the improved data have remained unchanged even 6 months later from the date of the treatment beginning.

**Conclusion**

Despite the fact that at present most experts believe that surgery techniques used to treat IHD are considered to be rather effectively in elimination of occlusions in the blood vessels, however the application of this approach cannot prevent further progression of an atherosclerotic process, since homeostasis disorders, which form the basis for atherogenesis, remain unaffected. Threatening recurrence of angina pectoris after surgery or surgical radiography, the probable MI recurrence, the necessity of completion of repeated more dangerous surgery, despair of a patient in case of his/her affected distal vascular bed can impose the condition to search for fresh methods of prevention of coronary atherosclerosis and vascular damages of other localization [3, 4, 6, 11].

Our completed studies have demonstrated that the use of PP within the framework of the complex therapy of the patients suffering from exertional angina functional class III-IV makes a favorable effect on clinical signs of the disease and the relevant data on the morphofunctional state of the cardiovascular system in this category of the patients.

### Table 3

Dynamics of heart rate variability values in patients with stable exertional angina functional class III-IV: the standard treatment vs. standard treatment approach including PP (M±m)

<table>
<thead>
<tr>
<th>Data</th>
<th>Reference group (n=32)</th>
<th>Main test group (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7 days</td>
<td>1 month</td>
</tr>
<tr>
<td>STE episodes</td>
<td>3,16±0,62</td>
<td>2,90±0,51</td>
</tr>
<tr>
<td>STD</td>
<td>142,2±8,3</td>
<td>138,5±7,2</td>
</tr>
<tr>
<td>episodes</td>
<td>1,97±0,40</td>
<td>1,95±0,34</td>
</tr>
<tr>
<td>VE</td>
<td>435,2±87,7</td>
<td>415,1±80,9</td>
</tr>
<tr>
<td>SVE</td>
<td>58,2±17,0</td>
<td>57,4±16,4</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>107,3±12,4</td>
<td>112,0±13,6</td>
</tr>
<tr>
<td>SDANN (ms)</td>
<td>98,8±12,4</td>
<td>101,2±13,6</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>61,5±13,0</td>
<td>63,1±13,0</td>
</tr>
<tr>
<td>VLF</td>
<td>1833±482</td>
<td>1857±534</td>
</tr>
<tr>
<td>LF (ms2)</td>
<td>994,5±203,1</td>
<td>989,3±207,0</td>
</tr>
<tr>
<td>HF (ms2)</td>
<td>785±143</td>
<td>854±165</td>
</tr>
<tr>
<td>L/H</td>
<td>1,261±0,351</td>
<td>1,109±0,311</td>
</tr>
</tbody>
</table>

Note: * - variances are plausible (at p<0,05) referred to the respective level in the reference group.
It is known that the main mechanisms of atherogenesis are hypercoagulation in the coronary arteries, deficit of fibrinolysis factors, activation of thrombocytes, damage of the coronary vessel intima, dysfunction of endothelial cells and the NO production. The activation of the full spectrum thereof takes place in the acute phase of atherogenesis [10, 12]. Taking into account all the above, we can arrive at a conclusion that PP, designed to eliminate the widest range of pathogenic agents and substances, shows most pronounced clinical effect in patients with unstable or progressing angina pectoris. This phenomenon has been supported by the results not only of our study, but also by the evidence data presented by other researchers [1].

As to pathogenesis of developing pathological damages in blood vessels, a role of chronic inflammation, inducible and maintainable by a variety of infection agents, cannot be excluded [3, 8, 12]. According to most advanced concepts, a local (in an atherosclerotic plaque) and a systemic inflammation play their fundamental role in developing atherosclerosis and complications of the latter [7-10]. The presence of hemodynamically significant stenosis cases of the vascular bed in patients is reported both for a low cholesterol level and a low atherogenicity index. Our assessment of the echocardiographic parameters in the examined patients has demonstrated that there is a tendency to the normalization of the above parameters with a more pronounced effect in the main test group. Improved echocardiographic characteristics in the chronic heart failure patients functional class III-IV upon completion of their PP-integrated therapy have been reported within the 1- to 6-month period: there have been significant changes in the parameters detected, as compared with those in the reference group, which are as follows: the EDV and the ESV values have been decreased; the ejection fraction value has been increased, and the Ve index has been reported to be higher. The clinical effect of plasmapheresis has been revealed at the early stages of the treatment and remained unchanged even 6 months later. The comparison study of the data collected in the above two groups bears witness to the fact that an integration of plasmapheresis into the combined therapy of the patients leads to more pronounced favorable shifts in the echocardiography examination data.

Our HRV analysis has shown that there are changes in some spectral power analysis data. In particular, in the patients of this category we have recorded an increase in shares of the Very Low and High Frequency waves that has indicated an elevated activity of the parasympathetic nervous system. The variance of the HRV parameters recorded on day 7 from the beginning of the treatment has remained unchanged later: upon expiration of 1 month to 6 months from the beginning of the standard approach therapy in chronic IHD patients, respectively. In general, the comparative study of the Holter monitoring results obtained in the group of the patients who have been treated according to the standard approach to therapy versus those who have received the plasmapheresis-added therapy have shown that the latter has many points in its favor: the patients of the main test groups have been characterized by the reduced occurrence rate of ST depression and elevation episodes and VE and SVE events. Significant differences have been detected in the data profiles pertaining to the spectral analysis data on the HF, LF components and the LF/HF ratio.

So, we may conclude that the offered introduced method as described above has demonstrated its safety for the specified category of the patients; the method shows its clinical and laboratory-related efficacy, so that it makes possible to integrate the PP option in the framework of other therapy schedules. We should note that the applicability of the method is cost-effective: it can be easily introduced in practice by a wide range of hospitals and treatment institutions, which focus on treatment of IHD, including ambulance entities.

Statement on ethical issues
Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest
None declared.

Author contributions
The authors read the ICMJE criteria for authorship and approved the final manuscript.

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