ВЕСТНИК
САНКТ-ПЕТЕРБУРГСКОГО УНИВЕРСИТЕТА

Том 16
Выпуск 3

2021
Сентябрь

МЕДИЦИНА

ВЕСТНИК ЛЕНИНГРАДСКОГО УНИВЕРСИТЕТА ОСНОВАН В АВГУСТЕ 1946 ГОДА
ЖУРНАЛ «ВЕСТНИК СПбГУ. МЕДИЦИНА» ВЫХОДИТ В СВЕТ С 2006 ГОДА

Vestnik of Saint Petersburg University. Medicine. Volume 16. Issue 3. 2021

СОДЕРЖАНИЕ

Учредитель: Санкт-Петербургский государственный университет

На журнал «Вестник Санкт-Петербургского университета. Медицина» можно подписаться по каталогу «Пресса России». Подписной индекс 36430

Свидетельство о регистрации СМИ No. ФС77-73018 от 6 июня 2018 г. (Роскомнадзор)

Главный редактор *П. К. Яблонский*, д-р мед. наук, проф.
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Дата выхода в свет .
Формат 70×100$^{1}/_{16}$. Усл. печ. л. 6,4. Уч.-изд. л. 6,5. Тираж 25 экз. Заказ No. . Цена свободная.

Адрес редакции: 199034, Санкт-Петербург, Университетская наб., 7–9.
Адрес Издательства СПбГУ: 199004, Санкт-Петербург, В. О., 6-я линия, д. 11.
Тел./факс 328-44-22

Типография Издательства СПбГУ. 199034, Санкт-Петербург, Менделеевская линия, д. 5.

INTERNAL DISEASES

UDC 616.72-002.77+616.16-007.64-079.4

Rheumatoid arthritis associated with Rendu — Osler — Weber disease: Second description*

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For citation: Carvalho J. F. de, Maia Rodrigues C. E., Freitas Zerbini C. A. de, Churilov L. P. Rheumatoid arthritis associated with Rendu — Osler — Weber disease: Second description. *Vestnik of Saint Petersburg University. Medicine*, 2021, vol. 16, issue 3, pp. 147–152.
https://doi.org/10.21638/spbu11.2021.301

The article presents second ever published description of rheumatoid arthritis case co-morbid with Rendu — Osler — Weber disease (hereditary hemorrhagic teleangiectasia) in a 63-years-old female patient. The aim is describing the first case report of a patient who after a confirmed hereditary hemorrhagic teleangiectasia diagnosis developed rheumatoid arthritis one year later. Historical data and brief pathophysiological characteristic of both diseases and their possible intermingle are included: (i) mutant genes in hereditary hemorrhagic teleangiectasia all encode proteins involved in the TGF-beta signaling pathway, and increased plasma levels of TGF-beta-1 and vascular endothelial growth factor have been seen in such patients; (ii) TGF-beta plays a role in the development of synovial cell proliferation, inflammation, and angiogenesis in rheumatoid arthritis; (iii) TGF-β regulates thymic T-cell selection, inhibits cytotoxic T lymphocyte (CTL), Th1-, and Th2-cell differentiation while promoting peripheral

* Contribution of L. P. Churilov was supported by the grant of the Government of Russian Federation for state support of scientific research carried out under the supervision of leading scientists, agreement 14.W03.31.0009.

Treg-, Th17-, Th9-, and Tfh-cell generation, and T-cell tissue residence in response to immune challenges, all essential for pathogenesis of rheumatoid arthriitis. The defect in its reception as well as its compensatory increased blood content theoretically can alter autoimmunity thus facilitating in Rendu — Osler — Weber disease patients the development of systemic autoimmune diseases.

Keywords: rheumatoid arthritis, Rendu — Osler — Weber disease, hereditary hemorrhagic telangiectasia.

Introduction

Rheumatoid arthritis (RA) is the most common systemic autoimmune rheumatic disease, occurring in 0.5 to 1 % of the population [1]. It is characterized by polyarticular involvement, which mainly affects the peripheral joints and can lead to major deformities. There are extra-articular manifestations described in this illness, such as secondary Sjögren's syndrome, rheumatoid vasculitis, amyloidosis, pleuritis and others [2]. It has been first medically described in Europe in 1800 by a French physician Augustin Jacob Landré-Beauvais (1772–1840). Paleopathological data from Americas witnessed for existence of RA among ancient rooted population of New World, but similar data are absent or doubtful for the ancient bones of the Old World, hence there is an assumption that RA was imported from Americas to Old World with some unknown antigens/pathogens and habit of smoking not earlier that in late XV — early XVI centuries [3].

Rendu — Osler — Weber disease (ROW) or hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder with varying penetrance and expression. The genetic mutations identified for the majority of ROW cases alter the expression of receptor proteins [endoglin (ENG) and activin receptor-like kinase 1 (Alk-1)], both involved in transmission of signals from transforming growth factor-beta 1 and/or 3 (TGFβ-1,3). The last two autacoids control the growth and functions of endothelial cells during angiogenesis [4]. For the first time ROW was differentiated from hemophilia and described in details as a distinct entity by French physician Henri Jules Louis Marie Rendu (1844–1902), although several cases of the illness were reported earlier in Britain [5]. The essential contribution from the Canadian-American physician William Bart Osler (1849–1919) was a series of cases with first postulation of the familiar nature of disease [6]. A bit later British physician Frederick Parkes Weber (1863–1962) amplified its clinical description [7]. The disease belongs to vasopathias and is characterized by hemorrhagic syndrome with diffuse telangiectasias mainly on the face and hands, and may also be present as arteriovenous fistulas in organs, such as the brain, liver and intestine. Sometimes lung vessels are involved with pulmonary hypertension. It does not have a specific treatment. The diagnosis is made by characteristic signs and symptoms: facial telangiectasia with involvement of hands or oral cavity; recurrent epistaxis; arteriovenous malformations with visceral involvement; and a positive family history. Diagnosis is confirmed upon the presence of at least three of these manifestations. Intestinal involvement may be aggravated by adenomas and even adenocarcinomas [4; 8]. A patient with RA associated with ROW was previously described in the literature only once [9].

So, this article aimed on describing the first case report of a patient that after a confirmed diagnosis of ROW developed RA one year later.

Case description

A 63-years-old female patient was diagnosed with intestinal mucinous adenocarcinoma in 2008. She was submitted to intestinal and regional lymph node resections and also treated with 6 cycles of chemotherapy with oxaliplatin and fluoracil. These drugs were interrupted due to liver toxicity, and the liver biopsy was compatible with vaso-occlusive disease. At the time, she evolved with several recurrent episodes of intestinal bleeding and started episodes of epistaxis, with normal platelet count. She underwent colonoscopy that revealed vascular ectasias, and received blood transfusions on 10 different occasions. Hemostasis was performed with argon laser (2 sessions). The angiotomography of the abdomen revealed an enlarged liver with an increased caliber of the hepatic artery. There was a spiral aspect of its intrahepatic branches with associated arteriovenous fistulas visualized throughout the parenchyma and some areas with small nodules. An enlarged portal vein was also detected. The cerebral angiotomography ruled out involvement of brain vessels. Pulmonary angiotomography showed arteriovenous fistula in the upper lingual region. This area was embolized in 2017, evolving after one week to a pulmonary infarction. Dermatoscopy revealed telangiectasias on her fingers, tongue and lips (Figure *a, b*). She had a family history of epistaxis in his father and two brothers, one of them with hemoptysis and diagnosis of pulmonary arteriovenous fistula. The HHT disease-associated gene testing was positive for heterozygosis state for the c1330–31dupGT germ line mutation in exon 9 of the Alk-1 gene. The patient fulfilled the diagnosis criteria for ROW [4; 8], in fact, she had recurrent epistaxis, telangiectasias in her face, hands and oral cavity; arteriovenous malformations on her lungs; and a positive family history. Her adenocarcinoma also maybe mechanistically related to ROW with intestinal involvement. She evolved well, without further episodes of intestinal bleeding, maintaining mild episodes of epistaxis.

But in 2013, she sought a private clinic with polyarthritis and diffuse joint pain initiated in 2009. On examination, she had polyarthritis including wrists, all metacarpal-phalangeal and proximal interphalangeal joints, in addition to knees and ankles, associated with morning stiffness which lasts 60 minutes. The laboratory tests revealed: anti-citrullinated protein antibody 130 IU/mL and rheumatoid factor 445 U/mL, erythrocyte sedimenta-

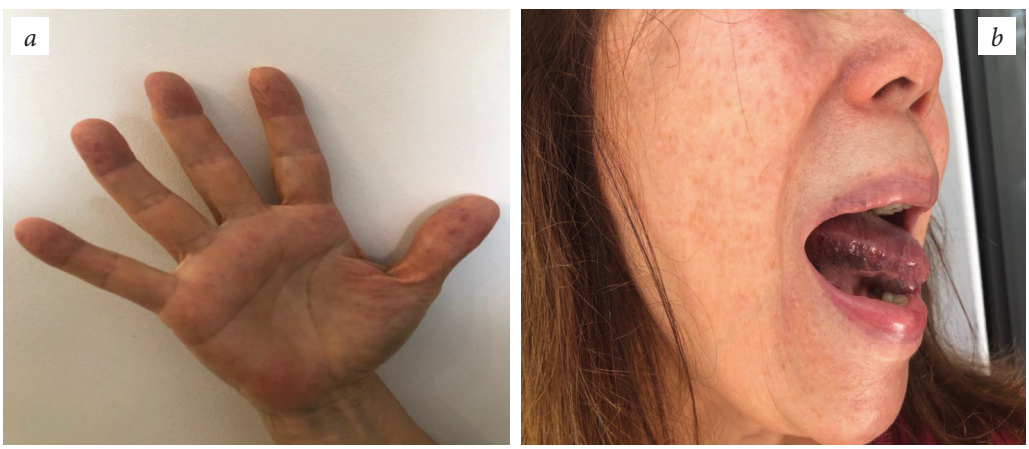

Figure. Photographs from the patient showing telangiectasias on her (*a*) fingers and hand, and (*b*) on her tongue and lips

tion rate 108 mm/hour and C-reactive protein of 22 mg/dL. A diagnosis of rheumatoid arthritis was performed. Due to the anamnesis of neoplastic, liver and gastrointestinal alterations, treatment with rituximab 1g was chosen and repeated after 15 days, and subsequently administered each 6 months. Purified protein derivative skin test for tuberculosis was negative and chest X-ray was normal. The patient received 12 cycles (2 applications each 6 months) and achieved a complete clinical remission, without signs of arthritis and with C-reactive protein level <0.05 mg/dL. Currently, she stays on maintenance of rituximab and on vitamin D 1,000 IU/day, melatonin 3 mg for insomnia, omega-3 unsaturated fatty acids 1g, as well as probiotics and others vitamin supplements. Sporadically, it presents mild epistaxis, without any episode of gastrointestinal or pulmonary bleeding.

Discussion

A case report describing a patient with glucocorticoid-induced ROW was found in the literature [10]. But this is distinct from the case of our patient since in her ROW appeared before the diagnosis of RA and the patient had no previous chronic condition for which she could use corticosteroids for a long term.

Regarding joint involvement in ROW, only cases of septic arthritis, algodystrophy of the upper extremity and pseudo-hemarthrosis were described. In fact, vascular telangiectasis in joints may favor the interference of microorganisms and bleeding [11–13]. Reinforcing this findings, a study observed the need for hospital admittance in a group of 73 ROW patients and 219 matched controls during a 20 years follow-up period and concluded that ROW patients had an increased probability of infections in joints and bones and of bleeding episodes. However, the incidence of thromboembolisms, cerebral abscesses and other conditions commonly considered to be related to ROW was comparable between the patients and the controls [14].

Interestingly, there is a description of ROW in other rheumatic diseases, such as Sjogren's syndrome, primary biliary cirrhosis, and scleroderma [15]. Telangiectasias may also be present in the limited form of scleroderma, but the clinical symptoms and other signs of this disease make its differential diagnosis with ROW very easy. It is possible that one of the pathophysiological mechanisms of telangiectasia — both in the limited form of scleroderma and ROW may involve ENG, a glycoprotein that makes up endothelial nitric oxide, which has been found to be altered in patients with scleroderma [16]. Furthermore, some possible pathogenetic explanations of the HHT and RA association might be:

— HHT mutant genes all encode proteins involved in the TGF-beta signaling pathway, and increased plasma levels of TGF-beta-1 and vascular endothelial growth factor have been seen in HHT patients [4];
— TGF-beta plays a role in the development of synovial cell proliferation, inflammation, and angiogenesis in RA.
— TGF-β regulates thymic T-cell selection, inhibits cytotoxic T lymphocyte (CTL), Th1-, and Th2-cell differentiation while promoting peripheral Treg-, Th17-, Th9-, and Tfh-cell generation, and T-cell tissue residence in response to immune challenges [17].

The defect in its reception as well as its compensatory increased blood content theoretically can alter autoimmunity thus facilitating in ROW patients the development of systemic autoimmune diseases.

Could targeting TGF-β-signaling then be a treatment strategy for both conditions? Future studies are desired in this field.

In conclusion, this is the second description in the literature of a patient with ROW disease who presented RA, after one year of evolution.

Ethical statement

The authors declare that they followed the World Medical Association Declaration of Helsinki in this study. An informed consent was obtained from the patient for publication of the case. Images used do not uncover a personality of patient.

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Received: March 8, 2021
Accepted: September 30, 2021

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Prediction of the fact and degree of coronary artery disease using the processing of clinical and instrumental data by artificial intelligence

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For citation: Abdualimov T. P., Obrezan A. G. Prediction of the fact and degree of coronary artery disease using the processing of clinical and instrumental data by artificial intelligence. *Vestnik of Saint Petersburg University. Medicine*, 2021, vol. 16, issue 3, pp. 153–158.
https://doi.org/10.21638/spbu11.2021.302

Aim of the study was to analyze the possibility of using neural network analysis to predict the severity of coronary bed lesion. The study was also designated to determine the performance and accuracy of the trained neural network model receiving input as the structured data and EGG images with the parameters and leads positioning differ from the training sample, and also to compare the efficiency of detecting transient myocardial ischemia with traditional diagnostic methods, such as 24-hour Holter monitoring, treadmill test. Neural network analysis of the available clinical, laboratory and instrumentation data allow to configure the network parameters for further prediction of coronary artery disease. The results obtained in the form of an AUC score allow to consider this method to be effective in the coronary artery disease diagnosis using recorded ECG tape with parameters and lead positioning differ from initial training sample. The efficiency of transient myocardial ischemia detection on the training sample of the trained neural network is higher in comparison with traditional diagnostic methods, such as 24-hour Holter monitoring, treadmill test.

Keywords: coronary arteries, neural networks, deep learning, ECG.

Introduction

According to the 5th edition of the European Cardiovascular Disease Statistics (published in 2017 by the European Society of Cardiology (ESC)), cardiovascular disease (CVD) is the first cause of mortality and morbidity in Europe. In 2015, more than 85 million people on the continent suffer from cardiovascular disease (48 % of men and 52 % of women), resulting in 3.9 million deaths (45 % of all causes of death). In the European Union (EU), 49 million people suffered from cardiovascular diseases with more than 1.8 million deaths (European Cardiovascular Disease Statistics 2017). These findings support that cardiovascular diseases, despite significant advances in diagnosis and treatment, are still the most common cause of morbidity and mortality in Europe. Early accurate diagnosis and prediction assessment are key factors to improve and optimize CVD outcomes.

The development of mathematical methods and hardware allows to use much more progressive algorithms than standard ones — artificial neural networks. The operating

principle based on fuzzy logic. Neural networks are machine-learning method, modeled on the way human processing information [1]. Working with a wealth of input data led to the widespread use of neural networks in numerous areas of medicine [2].

Each neuron (node) in the network stores a numerical value, and all of them form the network architecture. The connection between neurons governors using weight matrices. The last layer encodes the desired results. A neural network containing more than one hidden layer is defined as "deep", which allows to use multiple level abstractions [3].

Machine learning methods include technologies and algorithms that could improve the work of cardiologist as the amount of data available in clinical practice has significantly increased.

Potentially, it could facilitate and make each stage of patient management more effective [4].

Materials and methods

The study included 130 patients, who underwent elective or emergency coronary catherization.

The indications for coronary angiography were verified according to the recommendations of the European Society of Cardiology (EOC). The study was carried out in accordance with Good Clinical Practice and Declaration of Helsinki principles. Inclusion and exclusion criteria were defined.

Key inclusion criteria:

— signing the informed consent prior to the study, including the statistical processing of medical history data;
— aged over 18 years;
— indications (elective or emergency) for coronary catherization;
— recorded electrocardiography (25 mm/s) one day before / or less before the performed coronary catherization.

Key exclusion criteria:

— ECG identification of arrhythmias as the atrial fibrillation, AV nodal reentrant tachycardia, ventricular tachycardia while recording;
— previous stenting and / or coronary artery bypass grafting;
— pronounced disturbances on the recorded ECG;
— registration of ECG more than 24 hours before coronary catherization;
— any surgical or medical state that, according to the researcher, could significantly interfere the work of machine learning algorithm in relation to the accuracy of the results.

The doctor, conducting the study, analyzed the medical record data (complaints, anamnesis, objective, laboratory and instrumental data) and download these results into a machine learning database in a binary format.

At the first stage of data collection for each case, structured parameters were entered into a tabular form, as well as the ECG image in jpeg format into the database. Numerous morphometric, objective, laboratory and instrumental data of the patients were used to train neural networks, such as: age, gender, diagnosed acute coronary syndrome (ACS) or

chronic coronary syndrome (CCS), ST segment pathology on the ECG, the presence or absence of concomitant pathology (diabetes mellitus, hypertension, obesity, anemia, previous stroke, atherosclerosis, arrhythmias, dyslipidemias), aggravated heredity, bad habits (smoking, alcohol abuse), stress factors, low physical activity, menopause, increased nutritional intake.

The abovementioned factors were filled in a structured binary form (0, 1) in a tabular format. Registration of ECG on a sample, developed for a neural network training, was carried out using one type of apparatus and the record was transmitted to the machine learning operator in jpeg format. Thus, 22 parameters (key features) were used to develop a neural network learning algorithm.

Neural network was trained on the data obtained from the analysis of coronary angiograms. As "targeted" values were taken: performed stenting or recommended CABG based on coronary catherization, atherosclerosis, left main coronary artery stenosis, left main coronary artery subocclusion, anterior interventricular artery occlusion, anterior interventricular artery subocclusion, anterior interventricular artery stenosis, circumflex artery occlusion, circumflex artery subocclusion, circumflex artery stenosis, right coronary artery occlusion, right coronary artery subocclusion, right coronary artery stenosis.

The degree of the coronary artery stenosis was filled in the table in numerical form as a percentage, then converted to binary form (1 — stenosis more than 50 %), the rest of the parameters were filled in binary form according to the presence or absence of lesion. The above "targeted" values were predicted by a trained machine learning algorithm.

The algorithm had to solve the coronary arteries classification problem, to predict the absence or presence of lesion. The neural network was used to solve the classification problems, receiving input as the structured data and images and providing output as a multifactorial classification of the main coronary arteries. The ratio for training and testing was 100/30.Predicting and results evaluation were performed on a test sample.

Python libraries was used for designing a neural network architecture (pandas — for tabular data; TensorFlow — for neural networks constructing and their training). Supervised learning method was used on the available data, where the outcomes were known (coronary angiography data), and neural network parameters were adjusted to minimize the error.

The analysis of structured tabular data of the training sample, including 100 patients, was carried out. The average age of the patients was 64 years (from 31 to 89 years), 52 male patients and 48 female patients.

The men median age is less than that of women. In 62 out of 100 patients was verified ACS, ST segment elevation was diagnosed in 19 patients with ACS. Typical anginal pain was observed in 53 out of 62 patients with ACS, as well as in 14 patients without ACS, mainly with chronic coronary artery disease in medical history. Type 2 diabetes had 28 out of 100 patients. In most of cases was observed hypertension. Atherosclerosis was verified in 44 patients. Almost 25 patients had cardiac rhythm disturbances, such as the atrial fibrillation, Ryan high-grade ventricular premature beats. In 27 patients was verified obesity. Anemia of varying severity was observed in 18 cases; 5 patients suffered from acute cerebrovascular accident; 36 patients complained of dyspnea; in 27 cases was observed an increased level of cholesterol. Alcohol abuse was determined in 3 patients, then tobacco smoking in 24 patients; 32 patients in the «training» sample regularly experience

psycho-emotional overload; 32 patients had low physical activity and leading a sedentary lifestyle; 24 patients had increased nutritional intake.

The study was also designated to determine the performance and accuracy of the trained neural network model receiving input as the structured data and EGG images with the parameters and leads positioning differ from the training sample. Patients of the test sample underwent ECG on the devices of various manufacturers. Speed of ECG recordings, amplitude and leads positioning were determined randomly. ECG tapes for each case were converted into digital jpeg format using a portable camera.

Each patient of the test sample underwent 12-channel Holter daily monitoring and treadmill test. The detection results of transient myocardial ischemia were filled in the table for each method separately. (0 — absence of transient ischemia, 1 — presence.)

The assessment of the accuracy of lesions prediction of the main coronary arteries was carried out based on the CT coronary angiography data, the efficiency comparison of transient myocardial ischemia detection was conducted on the basis of prediction calculation of necessity to perform the revascularization of the coronary arteries by the neural network analysis method and the results obtained during 24-hour Holter monitoring, treadmill test.

Results

The neural network simultaneously received input as the ECG images (size of the digital three-dimensional matrix was $200 \times 200 \times 1$) and structured tabular data. As the output, the neural network predicted multilevel values of main coronary arterial lesions in the probabilistic form.

As the neural network layers for images processing were used fully-connected, convolutional, batch normalization and dropout layers, while for structured data processing was used only fully-connected layers. Within the neural network was taken concatenate layer for generalizing images and dataset weight. After concatenate layer, there are two fully-connected layers. An input layer includes 13 neurons for predicting each parameter. «Adam» (adaptive learning rate optimization algorithm calculating an exponential weighted moving average of the gradient and squared gradient) was used as an optimizer, cross entropy as a loss function.

Training was performed on 100 "epochs" (one epoch = one forward pass and one backward pass of all the training examples). «Batch» size (number of training examples per one iteration)-8, validation sample size is 0.1 Parameters and structure of the neural network was selected empirically. AUC (area under the ROC curve) was chosen as a starting metric for assessing the model quality.

Prediction of the main coronary arterial lesions was carried out. On a test sample including 30 patients, the AUC score was 0.87, where the accuracy was 96 %, precision was 76 %, recall was 71 % and the fl score — 74,1 %.

It was carried out the efficiency comparison of transient myocardial ischemia detection based on the prediction calculation of necessity to perform revascularization of the coronary arteries by the neural network analysis method and the results obtained during 24-hour Holter monitoring, treadmill test. Results of the neural network analysis method: accuracy 93 %, precision 60 %, recall 100 %, AUC score 96 %, f1 score 75 %, 24-hour Holter monitoring: accuracy 87 %, precision 33 %, recall 33 %, AUC score 63 %, f1 score 33 %, treadmill test.: accuracy 70 %, precision 12 %, recall 33 %, AUC score 54 %, f1 score 18 %.

Discussion

In modern medicine, decision-making is a complex process based on the availability of objective and reliable evidence, access to knowledge, as well as on the correct interpretation of the available data, considering the risk-benefit balance for the patient.

Prediction of the likelihood of a cardiovascular event for a relatively long period of time has become an important aspect of the patient's treatment. Annually, numerous models of assessing cardiovascular risk are designed by the researchers, the majority of which are based on the data obtained from clinical and registry-based studies.

However, only a small part of such models is used in everyday clinical practice. Due to this, qualitatively different approach is of a high importance.

In the present study, a relatively small amount of data was used: 22 parameters, ECG images from 130 patients. As a result, a neural network architecture was designed with a small number of parameters.

The result of multilevel classification of suggested lesions for each major coronary artery by the chosen neural network architecture confirmed the effectiveness of the model (AUC = 0.87). The designed neural network analysis model allow to sufficiently predict the lesion of the main coronary arteries on the basis of structured data and ECG images significantly differ by lead positioning, recording method from ECG images in test samples.

The accuracy of detecting transient myocardial ischemia, determined by neural network analysis and obtained in order to predict the need for coronary revascularization, is higher than that of traditional diagnostic methods, such as 24-hour Holter monitoring and treadmill test. The obtained results suggest a potential practical application of the neural network analysis method in clinical practice.

Conclusion

Neural network analysis of the available clinical, laboratory and instrumentation data allow to configure the network parameters for further prediction of coronary artery disease. The trained neural network predicts the main coronary arterial lesions with precise accuracy — 76 %, AUC score 0.87. The available high accuracy of the trained neural network model, observed in the test sample, based on the input structured data and recorded ECG with the parameters and lead positioning differ from initial training sample, allow to consider this method to be effective in the preliminary diagnosis of the main coronary arteries disease regardless the ECG machine model.

The detection efficiency of the transient myocardial ischemia in the abovementioned test sample is higher in the trained neural network, than in traditional diagnostic methods, such as 24-hour Holter monitoring and treadmill test.

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Received: May 31, 2021
Accepted: June 24, 2021

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NEUROLOGY. NEUROSURGERY. PSYCHIATRY

UDC 616.831-005:616-036:616-092.11

Neurorehabilitation: Sanogenetic and pathogenetic foundations of innovative directions

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For citation: Tibekina L. M., Shaposhnikov A. N. Neurorehabilitation: Sanogenetic and pathogenetic foundations of innovative directions. *Vestnik of Saint Petersburg University. Medicine*, 2021, vol. 16, issue 3, pp. 159–170. https://doi.org/10.21638/spbu11.2021.303

The processes of sanogenesis and pathogenesis in patients with acute cerebrovascular accident occur simultaneously, starting with the acute period of stroke. In most cases, this is a single process viewed from different perspectives. Modern innovative areas of neurorehabilitation include the use of drug therapy, rehabilitation measures and mechanisms of sanogenesis and self-healing, which can be influenced by the methods used in the course of restoring the health of neurological patients. The organizational model of modern neurorehabilitation is based on an interdisciplinary multistage approach. The analysis of the relationship between patho- and sanogenetic reactions is important for the development of this organizational model. Exogenous therapeutic and rehabilitation measures form a single complex with endogenous factors of sanogenesis. These measures achieve the maximum effect only with the conscious active participation of the patient in the recovery process. The theoretical basis of the research is the concept of the theory of functional systems by P. K. Anokhin and the axiomatic theory of human health. The integration of these approaches is considered as the most general self-acting self-healing mechanism, concretized in the form of the concept of sanogenesis. Mechanisms for maintaining homeostasis are activated at all levels when a damaging factor occurs. Pathogenesis develops, becoming an integral part of the processes of sanogenesis.

Keywords: rehabilitation, sanogenesis, pathogenesis, theory of functional systems, theory of human health, innovation, stroke.

Introduction

Acute cerebrovascular accidents (ACVI) remain one of the most pressing health problems in the world. Stroke ranks second in mortality in the Russian Federation (RF), yielding to cardiovascular diseases [1; 2]. Stroke is 123 cases per 100,000 population an-

nually [3]. 31 % of stroke patients require outside help. Only 10–12 % of patients return to their previous work after a stroke [4; 5]. More than 450 thousand new cases of stroke are registered annually in the Russian Federation, despite the measures taken to reduce mortality from diseases of the circulatory system. Stroke doubles the risk of dementia in older people. Unfortunately, the global prospects for stroke are disappointing due to the increasing morbidity and mortality of patients, especially in countries with low living standards [6].

Patients who have undergone stroke, as a rule, require long-term rehabilitation.

To date, the first version of the organizational model of medical rehabilitation in Russia has been developed, and its individual blocks are being implemented [7]. The developed concept and system of organizing neurorehabilitation involves 3 stages and 3 levels of care for patients with lesions of the nervous system. This approach takes into account the severity of the patient's condition and his rehabilitation potential.

The updated models of medical rehabilitation have been developed in Russia taking into account the regulatory framework for neurorehabilitation. Strengthening the active role of the patient himself in the rehabilitation process is clearly visible in the framework of the adopted approaches. In fact, this means the activation of the process of sanogenesis, or more broadly — the activation of the forces of self-healing in the course of restoring health. Therefore, the *multidisciplinary rehabilitation team* (MDRK) includes not only clinicians, but also psychologists, educators, social workers and other specialists. The means and methods of rehabilitation used are increasingly based on self-organized mechanisms of sanogenesis [8].

The article discusses some theoretical issues of the direction of innovation in neurorehabilitation. These innovations are aimed at the optimal combination of drug therapy, rehabilitation measures and mechanisms of sanogenesis and self-healing in the course of restoring the health of neurological patients.

Sanogenesis in the rehabilitation of patients with brain damage

The solution of theoretical issues of neurorehabilitation plays an important role in improving the methods of rehabilitation of patients, incl. stroke victims. Neurorehabilitation seeks to achieve an optimal ratio of medical (medicinal) methods with rehabilitation measures. The conscious activity of the patient himself also plays an extremely important role in the healing process, because along with drug therapy, it is important to maximally activate the forces of self-healing, evolutionarily embedded in the natural essence of man [9].

In this regard, an increasingly active use of the concept of sanogenesis is an important and relatively new theoretical approach in the development of rehabilitology. Sanogenesis is usually understood as a complex of protective and adaptive mechanisms aimed at restoring impaired self-regulation of the body. It is obvious that sanogenetic mechanisms are regulated, on the one hand, by the nervous system (mainly the central nervous system), and on the other, by genetic regulatory programs [10]. In this interpretation, sanogenesis is one of the most important, but not the only form of manifestation of the mechanisms of human self-healing action [11]. The simultaneous development and interaction of the mechanisms of pathogenesis and sanogenesis is considered by many authors as an integral process of human self-healing, aimed at restoring the full functioning of all organs, systems and homeostasis of the patient [12–14].

Rehabilitation care is based on the use of differentiated medical and neuropsychological methods. These methods are part of a unified rehabilitation program and are applied in accordance with the stage of the disease [7; 15]. At the same time, the processes of sanogenesis proceed in a self-acting self-organized mode. The patient can contribute to obtaining a beneficial effect of sanogenetic mechanisms of self-healing at the maximum accessible level by his correct actions during rehabilitation measures.

Regulatory legal documents indicate the need for the earliest possible start of rehabilitation measures. Early rehabilitation should begin as early as the first 12–48 hours of a patient's hospital stay in the acute and acute period of stroke.

The basic principles of rehabilitation of patients with lesions of the nervous system are:

— multidisciplinary approach;
— continuity and phasing;
— consistency and duration;
— complexity;
— individualization of rehabilitation programs and their social orientation;
— active participation in the rehabilitation of the patient himself, his family and friends;
— monitoring the adequacy of loads and the effectiveness of rehabilitation [16].

These principles clearly demonstrate the orientation towards the individualization of rehabilitation programs, their social orientation. The patient's relatives and friends take an active part in the rehabilitation process. As a result, rehabilitation measures are increasingly focused on activating the processes of sanogenesis in the patient's recovery.

Drug therapy inevitably dominates at the first stage of rehabilitation in the acute period of stroke. The patient's life at this stage often depends solely on timely medical intervention, up to and including surgery. Rehabilitation measures, as such, come to the fore at the second stage of rehabilitation. At the first stage they are also important and contribute to the prevention of contractures, pain syndromes, thrombosis, congestion in the lungs, etc.

At the second stage, the emphasis is on rehabilitation activities carried out in a medical institution with the participation of MDRK specialists. The main task of the MDRK is the most effective activation of the processes of sanogenesis, or the forces of self-healing of a person.

Sanogenesis develops independently in a self-organized self-acting mode immediately after exposure to damaging factors. This can be, for example, cerebral ischemia or traumatic brain injury. The processes of pathogenesis and sanogenesis always proceed simultaneously. This usually happens before the patient begins to receive medical attention. In other words, sanogenesis occurs before the treatment started and continues continuously at all stages of providing assistance to the patient. From this point of view, the rehabilitation process can be considered as the maximum activation of the compensatory-adaptive mechanisms of sanogenesis during the restoration of the patient's health. Therefore, neurorehabilitation today presupposes the fastest possible start of rehabilitation measures directly at the first stage of the acute period of the disease. This approach is fully consistent with the understanding that the processes of sanogenesis begin simultaneously with the processes of pathogenesis of the disease. Rehabilitation measures stimulate the

development of "self-healing" processes of sanogenesis most effectively if they are started as quickly and competently as possible.

The Regulation on MDRK (Appendix 2 of the Order of the Ministry of Health No. 788n dated July 31, 2020) provides for the establishment of a rehabilitation diagnosis. The diagnosis should take into account the patient's active participation, environmental factors, and the patient's personality factors, which are determined on the basis of the International Classification of Functioning (ICF). The modern structure of rehabilitation diagnosis gives a fairly accurate description of the patient's condition and life limitations. The diagnosis includes the influence of environmental factors, personal factors and their changes in the process of carrying out measures for medical rehabilitation. The accuracy of the diagnosis is important both when moving from one stage of treatment to another, and for ensuring the continuity of treatment in different medical institutions.

Structural and functional changes in brain damage

Restitution, regeneration, compensation and neuroplasticity are important mechanisms of sanogenesis. Restitution provides initial restoration (in fact, self-healing) of function, i. e. true resumption of the activity of partially damaged and functionally inhibited nerve structures. For example, the phenomenon of diachisis, discovered in 1897 by C. von Monakow.

Regeneration of nerve structures and organs functionally associated with them occurs later (for example, the regeneration of peripheral nerves after injury and the resumption of the work of the muscles they innervate). Regeneration is also a self-acting self-organized process of manifestation of the self-healing forces of the body. Compensation is the replacement of a lost function at the expense of functionally similar or other structures. Compensation mechanisms also operate in a self-organized manner.

Early recovery after brain damage is associated with regression of local cerebral edema, resorption of decay products and inflammatory mediators formed as a result of ischemia and necrosis, improved blood flow in the infarction zone, and restoration of the functioning of partially damaged neurons.

Compensatory changes associated with neuroplasticity occur in parallel with these processes or somewhat later. New synaptic connections are formed in the brain. The structures of the brain that were not previously involved in the implementation of the impaired function are involved in its implementation, there are changes associated with diachysis. The plasticity of the nervous system is understood as the ability of the nervous tissue to independently restore its function through qualitative and quantitative neuronal rearrangements, changes in neuronal connections and glial elements [17]. This process is one of the many mechanisms of sanogenesis. Nervous tissue is capable of independently changing the structural and functional organization. It has been established that self-acting sanogenetic processes of neuroplasticity in the central nervous system occur at the molecular, cellular, synaptic, anatomical levels, not only in the cortical regions, but also in the subcortical structures [18].

Different parts of the central nervous system have different neuroplastic potential for self-healing. The cerebral cortex is considered the most plastic part of the central nervous system, which is due to the variety of its constituent cellular elements and their connections. Macro-level neuroplasticity in the process of sanogenesis is associated with a

change in the network structure of the brain, which provides communication between the hemispheres and different areas within each hemisphere. At the micro level, changes occur in the neurons and synapses themselves. Plasticity can manifest itself both quickly and slowly at all levels. In this case, it is important to emphasize that neuroplasticity proceeds as a self-organized sanogenetic process. Thus, "fast neuroplasticity" activates previously unused horizontal connections in the cerebral cortex, as well as modulation of synaptic transmission [19; 20].

Plastic processes are accompanied not only by structural changes in synapses, dendrites, astroglia, neurons and capillaries. In parallel, molecular-genetic and biochemical mechanisms of influence on plasticity are activated through the production of biologically active substances of stimulating, inhibitory or modulating action [21]. These mechanisms underlie memory, learning, and recovery of the nervous system after injury.

Another type of neuroplasticity is sensitization, which manifests itself in an automatically arising amplification of the response to potentially dangerous damaging stimuli. This type of neuroplasticity can occur in the same synapses where habituation or addiction occurs (one of the simplest forms of neuroplasticity). It can be short-term and long-term. The reversible mechanisms of plasticity (habituation and sensitization) differ from long-term potentiation. This kind of plasticity results in permanent, long-term changes in the strength of synaptic connections. This mechanism underlies the self-restoration of the patient's cognitive capabilities: learning, acquisition of knowledge, skills, self-restoration of memory.

It has been proven that neurogenesis is possible in some parts of the brain. In an adult, such structures include the hippocampus and the subventricular zone [22; 23]. In the hippocampus, progenitor cells are located in the vascular-rich periventricular zone. In these zones, sanogenetic reactions in the form of neurogenesis are ongoing.

Neurogenesis is an important self-acting process of restoring brain tissue and the nervous system as a whole. It manifests itself in the form of cell proliferation, migration and cell differentiation. Outside the neurogenic zones of the brain, two forms of neurogenesis have been identified. The first is local neurogenesis associated with the activation of progenitor cells in response to pathological stimuli. The second is the migration of progenitor cells from neurogenic areas of the brain to damaged areas. When the central nervous system is damaged, the mechanisms of sanogenesis are manifested in the fact that the direction of cell migration changes independently: they leave the rostral migration flow and move to distant areas where neuronal death is detected [24; 25]. Progenitor cells replacing damaged neurons are located throughout the periventricular region of the forebrain [24; 26].

There is evidence of perivascular mesenchymal stem cells found in neurogenic and non-neurogenic areas of the brain in the perivascular spaces of adult animals and humans [24].

Perivascular mesenchymal stem cells have specific features. These include differentiation along the ectodermal or mesodermal pathway, immunomodulatory pro-regenerative ability (secretion of growth factors, angiogenesis factors, mitogens and cytokines), maintenance of tissue homeostasis, including the microenvironment of stem cells, etc.

The body's self-healing mechanisms are multifaceted. In addition to structural changes in the nervous tissue, dynamic shifts also occur. They are of a functional nature, spreading both directly in the lesion focus and at a distance from it [18].

It must be borne in mind that during rehabilitation, plasticity can manifest itself as a two-faced Janus. Plasticity is involved in the emergence and consolidation of both positive and negative (pathological) changes in the central nervous system. When mobilizing genetically programmed mechanisms of sanogenesis, damaging factors can form pathological systems. Such systems are possible as a result of inadequate rehabilitation measures. The properties and features of the formation of pathological systems have been studied in detail by G. N. Kryzhanovsky, his colleagues and students [14; 27; 28].

In relation to pathological systems in the body, there is a restructuring of the normal self-regulation of functional systems. Self-regulation can be aimed at eliminating a pathological system or establishing a new compensatory level of intrasystemic relations. Spasticity and other clinical symptoms may form by 3–4 weeks after stroke. Clinical neurology provides for the early use of methods that prevent the development of muscle hypertension and pathological attitudes. It is these factors that determine in the future the formation of contractures, pain syndrome and a decrease in the patient's functional capabilities [29].

Exogenous factors affect the mechanisms of sanogenesis, including the use of specific techniques by the participants of the MDC. This makes it necessary to constantly improve the skills of the members of the MDRK. Patients recover to varying degrees of impaired functions, including motor functions [30]. The first level is true "self-healing" with the return of impaired motor functions. It is possible in the absence of neuronal death, when the pathological focus consists mainly of inactivated cells. The second level is compensation with the main mechanism of functional restructuring and the involvement of new, previously unused brain structures. The third level is readaptation, or adaptation to an existing defect. At this level, patients use special means of technical rehabilitation (support canes, crutches, walkers, wheelchairs).

The strategy of rehabilitation therapy for patients who have suffered a stroke or TBI involves, first of all, the elimination or reduction of the influence of pathological systems that form persistent neurological syndromes. Such an impact is possible as a result of suppression of pathological determinants, destabilization of the pathological system and activation of antisystems. The optimal result is achieved by a combination of the mechanisms of sanogenesis and pharmacological and non-drug therapeutic effects [14; 30].

In this regard, at the stage of early rehabilitation, it is important to prevent the formation of stable pathological systems: contractures, pathological motor stereotypes and postures, arthralgias. A significant decrease in their severity is possible due to the activation of sanogenetic mechanisms and the destruction of pathological systems [31]. The role of a conscious purposeful activity of the patient himself in the prevention of the formation of stable pathological systems can hardly be overestimated.

The nature and degree of reorganization of neuronal connections is determined by the load exerted on them. The volume, intensity and time costs for each type of treatment and rehabilitation are determined by the specifics of the disease, the characteristics of its course, the severity of the consequences, the personal qualities of the patient, the degree of his psychological traumatization and social maladjustment. It has been shown experimentally that training in motor skills, depending on the intensity of the load, can contribute to the expansion of the area of cortical representation of the muscles involved [32–34]. But too active rehabilitation in the early period of stroke can have an unfavorable effect [35; 36]. Thus, forced loading on the paretic limb during the first 7–14 days from the onset of

stroke development led to a delay in the recovery of motor functions and an increase in the lesion focus [36]. This was explained by the additional release of glutamate and catecholamines, hyperexcitability of neurons in the perifocal zone, and imbalance between the processes of excitation and inhibition. In this case, excessive loads had a negative impact on sanogenetic mechanisms. The qualified work of the MDRK members plays a key role in avoiding this mistake.

The severity of compensatory-adaptive reactions may differ in patients of different ages. Thus, our studies [37; 38] showed that in patients of different age groups with ischemic stroke (IS) of moderate and mild severity, psychopathological disorders (anxiety, depression) had varying degrees of severity. In patients of young and middle age in the acute period of stroke, there were no significant differences in the dynamics of indicators of psychopathological status. On the contrary, in elderly and senile patients, there was a positive dynamics of these indicators. In elderly patients, a significant predominance of sympathetic tone in the cardiovascular system was revealed, which was not observed in middle-aged and elderly patients with a predominance of the tone of the parasympathetic nervous system.

So, in elderly patients, Kerdo's vegetative index was 19.3, while in old and middle age it corresponded to 1.3 and 9.3 ($p = 0.023$). The absence of this effect was especially clear in patients with IS and metabolic syndrome [39]. The use of a "questionnaire for identifying signs of vegetative changes" and a "study design for identifying signs of vegetative disorders" (A. M. Wein, 1991) showed that vegetative disorders had different dynamics in individuals of different age groups. In the middle-aged group, during the first week, the indicator changed from 21.5 ± 06 points to 19.0 ± 0.42 points ($p = 0.004$). The same indicators in the elderly group were equal to 26.8 ± 12.1 and 25.0 ± 14 points, respectively ($p = 0.2$). Significant gender differences were found in the depression scale scores. In men, the indicator corresponded to 46.0 ± 0.5 points, decreasing by the end of the week to 40.0 ± 0.61 ($p < 0.02$), and in women it changed from 45.1 ± 0.7 points to 42, 5 ± 0.5 ($p > 0.05$).

Emotional background and autonomic imbalance with impaired autonomic support for organs and autonomic reactivity can have a significant impact on the course of compensatory-adaptive reactions. This effect is poorly understood. In such patients (especially in young and middle-aged people), their psychoemotional status is of particular importance — the empathy of relatives and friends, surrounding staff is important.

Traditionally, the main attention in the preparation of rehabilitation programs is given to the morphological and functional characteristics of patients. Our research shows that personality traits and psycho-emotional status have an important influence on the patient's motivation for recovery. In turn, positive motivation activates the compensatory-protective mechanisms of sanogenesis [9].

On the other hand, it is necessary to take into account the factors that can delay the restoration of impaired functions. These are such personal factors of the patient as lack of motivation for rehabilitation measures; inadequate assessment by patients of the presence of a deficit of function; pain reactions; trophic disorders; depressive mood background; low tolerance to physical activity and the social level of the patient's family. There are also external factors that limit the patient's mobility, the degree of self-service, the fulfillment of the patient's natural functions; overprotection; lack of means of technical rehabilitation. Consideration and elimination (if possible) of these factors are also necessary for effective rehabilitation [16].

As we can see, modern neurorehabilitation is constantly looking for ways to optimally combine the methods of therapeutic rehabilitation and self-acting mechanisms of self-healing of the patient. A new direction on this path is the harmonious relationship of medical and non-medical health factors in the development of a full-fledged integral theory of human health. Integration of the methodology of health theory [9; 11; 40] and the theory of functional systems proposed by P. K. Anokhin looks very promising [41]. This allows us to consider in a new way the interaction of self-acting mechanisms of sanogenesis, on the one hand, and the system of therapeutic and rehabilitation measures, on the other.

The theory of functional systems in rehabilitation

The idea of the structural and functional organization of the brain underlies the theory of functional systems. The processes of self-organization and reorganization constantly occur in the human brain, the purpose of which is to achieve a useful result. According to P. K. Anokhin a useful result is the main system-forming factor of the functional system of the body (FSO). The author formulated the main features of the PSO as an integrative education:

— FSO is a central-peripheral formation, becoming a specific apparatus of self-regulation. PSO maintains its unity on the basis of cyclical circulation from the periphery to the centers and from the centers to the periphery;
— the existence of any FSO is certainly associated with obtaining a specific adaptive effect;
— the final effect determines one or another distribution of excitations and activities in the PSO as a whole.

An absolute sign of PSO is the presence of receptor apparatus. Receptor devices can be extensive afferent formations of the central nervous system, which perceive afferent signaling from the periphery about the results of an action. The theory of functional systems states that an integral organism unites a large number of interacting PSOs. The integration of the PSO takes place on the basis of nervous, humoral and informational mechanisms. The result is a stable constancy of the mechanisms of homeostasis, adaptation and adaptation to the environment. In fact, all of these mechanisms are included in the concept of sanogenesis in accordance with its definition. Note that P. K. Anokhin did not use the terms sanogenesis and self-healing, using the term "self-regulation".

P. K. Anokhin formulated a new approach to understanding the functions of the whole organism. Classical organ physiology has traditionally followed anatomical principles. The theory of functional systems assumes the priority of the systemic self-organization of human functions. These self-acting self-sufficient mechanisms function steadily from the molecular to the social level [9].

A person has several levels of organization of the FSO. Some PSOs act as self-organized mechanisms of sanogenesis (metabolic, genetic, homeostatic, etc.). Other PSOs function in the form of conscious life activity at the behavioral, mental and social levels [42]. All FSOs have fundamentally the same architectonics, including the result, the reverse afferentation from the result, the center and the executive elements. The central architectonics of the PSO includes the stages of afferent synthesis, decision-making, an acceptor

of the result of an action, an efferent synthesis, an action and a constant assessment of the results achieved using reverse afferentation. Each result of the PSO action automatically generates a flow of reverse afferentations, which represent the most important signs of the results obtained.

The described understanding of the universal self-organization of PSO mechanisms is used when carrying out treatment methods based on biofeedback mechanisms. The dynamic self-regulating process of the formation of the FSO is subordinated to obtaining a useful result. Insufficiency of the result can completely reorganize the existing FSO and form a new one. FSO according to P. K. Anokhin is a complex of selective involvement of the components of the system elements to obtain a focused useful result. Self-regulation of this process is an integral part of the body's self-healing process. Self-healing occurs by automatically switching on and activating the mechanisms of sanogenesis in the course of healing.

From the standpoint of the theory of functional systems, rehabilitation measures act as an effective external link that activates the functions of self-organized PSO. In this respect, the published first version of the axiomatic theory of human health (THH) [9; 11] is of interest. The THH methodology relies heavily on the FSO theory and expands it. The key concept of THH is the category "health".

A person is essentially self-sufficient in nature and contains everything in order to independently and fully exercise all his functions, to live and develop normally in society. This self-sufficiency is genetically fixed by evolution. Analyzing life through the prism of health, we see the integral property of self-healing inherent in a person.

The human sciences have not yet come to a single generalizing concept that encompasses all the mechanisms of self-healing and self-healing of a person. The THH development methodology considers a person in a holistic manner. The principle of integrity requires the presence of a generalizing concept in the conceptual apparatus of the THH, which includes in its content the systemic essence of all mechanisms of self-healing and self-healing of a person. It seems logical to consider health as such a generalizing integral concept in framework within the THH. In accordance with this, the following definition of the concept of health has been proposed. Health is a self-acting self-sufficient integral ability inherent in a person to fully function and self-reproduce at the cellular, tissue, organ, organismic, mental, social and spiritual levels. Health, as an integral ability for self-healing, is based on the self-organized action of the mechanisms of self-regulation, self-government, self-defense, sanogenesis and homeostasis. Health provides a person with self- restoration and self-healing after stress, injury and illness.

Health is an integral ability of an integral living organism, and not its specialized subsystem, function or group of functions. Healthy life can be viewed as the "ontogeny of health" from conception to death. Ontogeny of health is the ontogeny of functioning, restoration and reproduction of all self-healing mechanisms based on self-organization. The ontogeny of human health is based on self-organization. It is impossible to understand health and its evolution without understanding what self-organization is and how it works.

An axiomatic approach is at the heart of the creation of the THH. The specificity of the axiomatic approach made it possible to generalize and systematize the latest data in genetics, physiology, neurology, sociology of health, biophysics, quantum information theory and other sciences. This made it possible to introduce a number of new concepts

and develop a theoretical criterion for choosing factors that completely determine human health [11; 40]. The essence of the criterion is that this is the minimum set of irreplaceable factors that completely determine human health. The authors of the THH substantiated in the first approximation the hypothesis about the presence of 12 basic factors that completely determine human health.

The use of basic factors gives a powerful synergistic effect that some of the health factors cannot provide. This also applies to the factors of a healthy lifestyle, which are focused on the primary and secondary prevention of diseases of the cardiovascular system. Therefore, a promising area of neurorehabilitation is the patient's motivation to master self-healing techniques based on all basic health factors.

Thus, the integration of the theory of functional systems and the theory of human health seems to be a promising approach in the development of neurorehabilitology.

The disease usually affects many interrelated PSOs. In this regard, the assessment of various indicators of the body's activity in pathological conditions should take into account the systemic integration of physiological functions. When the structures of the brain are damaged, it is important to determine which stage of the systemic organization is impaired: afferent synthesis, decision-making, foresight or assessment of the results achieved. Disorders of afferent synthesis prevents the creation of a program of activity and a model of the required result. In case of violation of the reverse afferentation from the achieved result, there is no possibility of its adequate correction. This is often observed in patients with a pathological process in the frontal lobe. Excessive pathologically enhanced motivation and activation of the system make it uncontrollable, and the result of its activity has a pathological significance.

Rough disintegration in the activity of the FSO occurs when the suprasegmental structures of the autonomic nervous system are involved in the pathological process. These structures ensure the maintenance of homeostasis, the vegetative support of the activity of organs and systems, the adaptation of the organism to changing environmental conditions. The central vegetative apparatus is represented at the hemispheric, mesencephalic, bulbar and spinal levels and has a hierarchical organization [43].

CNS structures are not the only pathological determinant. It has been established that a pathological system, like pathodynamic integration, can cover different PSOs [14]. The same role is played by the enzymes of the intracellular signaling system, pathologically altered proteins, and dysregulatory or mutationally altered genes.

Conclusion

Analysis of the structural and functional changes occurring in the body with brain damage allows improving the methods of rehabilitation of patients with central nervous system damage. Self-organized mechanisms of sanogenesis are constantly functioning in the body (along with emerging pathogenetic processes). Their effectiveness increases significantly with conscious participation in the rehabilitation process of the patient himself. The mechanisms of sanogenesis are self-sufficient and immediately "turn on" automatically after the appearance of the lesion focus. The optimal combination of self-healing mechanisms with therapeutic and rehabilitation measures with the active participation of the patient himself ensures the healing process most effectively.

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Received: May 27, 2021
Accepted: June 16, 2021

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New possibilities of screening for mental disorders in cardiology practice

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For citation: Zadvorev S. F., Dorofeikova M. V., Petrova N. N., Yakovlev A. A. New possibilities of screening for mental disorders in cardiology practice. *Vestnik of Saint Petersburg University. Medicine*, 2021, vol. 16, issue 3, pp. 171–179. https://doi.org/10.21638/spbu11.2021.304

Aim of the study: validation of novel algorithm for screening of mental comorbidity in general medical practice. Based on retrospectively formed registry of patients, we assessed an effectiveness of the previously proposed Psycho-cardiac comorbidity Index. An external validation was provided, with subgroup analysis on cohort of patients who presented with suspected "Non-ST-elevation acute coronary syndrome" (N = 577), with assessment of psychopharmacotherapy prescription rate and prevalence of anxiety and depression. Another validation was carried out via comparison with patients with verified mental disorders (N = 235). A positive association was found between magnitude of Psycho-cardiac comorbidity index and Hospital anxiety and depression subscales ($r = 0.26$, $p < 0.001$ for anxiety subscale, $r = 0.17$, $p = 0.026$ for depression subscale), over-diagnosis of acute coronary syndrome at pre-hospital stage ($r = -0.27$, $p < 0.0001$), as well as with neurotic, affective and somatoform mental disorders (average Index 8.59 vs. 7.52 points, $U = 6040.5$, $p = 0.041$). The found pattern may be useful for clinicians for screening for patients who require a multidisciplinary approach to diagnosis and treatment.

Keywords: psychocardiology, acute coronary syndrome, screening of mental disorders, psychosomatics, anxiety, comorbidity.

Introduction

The mental disorders are highly prevalent in cardiology patients, with predominance of somatoform disorders and hypochondriasis (cumulatively over 30 % patients), as well as affective and anxiety disorders [1; 2]. The current evidence exists that almost two-thirds hospitalized patients with acute myocardium infarction (MI) demonstrate depressive symptoms, with 15 % prevalence of depressive episodes in patients with cardiovascular diseases (CVD), which is 2–3-fold higher compared to general population. Patients with heart failure (HF) demonstrate even hither burden of depression, reaching up to 20 %, depending on HF functional class. 15–20 % patients experience depressive episode after coronary artery bypass grafting [3]. Anxiety disorders are found in 7–20 % patients with chronic coronary artery disease (CAD) [4; 5], and phobic symptoms are 10 times more prevalent compared to general population [6]. Both anxiety and depression are associated

with risk of severe complications and death in patients with acute coronary syndromes (ACS) [7]. When diagnosed in time, mental disorders can be treated more effectively in cardiology patients, to increase their longevity and quality of life [8–10]. It was demonstrated that psychotherapy, mostly cognitive behavioral therapy, demonstrates mild to moderate 3-month improvement of symptoms in patients with non-specific chest pain without CAD [11]. In patients with verified CAD, the same intervention leads only to decrease in anxiety and depression [12]. Psychosocial assistance to stable CAD patients leads to improved quality of life, decrease in anxious and depressive symptoms and cardiovascular mortality.

Psychopharmacotherapy in practice of cardiologist was demonstrated to be efficient for correction of anxiety and depression in patients with MI [13] and with personal history of MI and pre-existed depressive symptoms [6]. Nonetheless, the prescription rate for psychopharmacotherapy is limited by concerns of drug-drug interactions [14].

Previously, we have proposed the Psycho-cardiac comorbidity index (PCI). An analysis showed that labile blood pressure, early manifestation of arrhythmias, female gender and multiple comorbidities are significant predictors for prescription of psychopharmacotherapy [15].

Aims of the study

Validation of a novel algorithm for screening of mental disorders in general medical patients by application of Psycho-cardiac comorbidity index on subpopulation of cardiology in-hospital patients; additional validation cohort of patients with verified mental disorders. Also, we investigated the potential additional role of an index in diagnostic protocol for patients presenting with suspected non-ST-elevation ACS (NSTE-ACS).

Methods

We carried out the retrospective observational two-center analysis of 956 medical records, forming 2 cohorts. For every patient, the PCI was calculated based on multiple linear regression, with the endpoint defined as prescription of psychopharmacotherapy for post-hospital stage. The formula of PCI was

$$PCI = 8 \cdot L + C + 3 \cdot F + 3\ (6) \cdot A,$$

where PCI — Psycho-cardiac comorbidity Index; L — labile or paroxysmal arterial hypertension, defined as rapid increase of blood pressure over once a week; C — comorbidity count; F — female gender; A — arrhythmias or palpitations with onset at the age under 55 (3 points) or under 50 (6 points) [15].

The PCI validation cohort included 721 patients hospitalized into cardiology department during September 2016 to November 2019 (56.7 % females), the recruitment was continuous. Of them, 577 presented with suspected NSTE-ACS. The baseline demographic and medical characteristics are presented at table 1 for validation cohort and at table 2 for NSTE-ACS subgroups.

The additional cohort contained 235 continuously recruited patients who underwent in-hospital treatment due to previously verified mental disorder without urgent indications for hospitalization (74.7 % females, mean age 66.0 ± 12.5 years).

Table 1. **Baseline characteristics of validation and additional group**

Parameter	Validation group	NSTE-ACS group	Additional group
Patients count	721	577	235
Females, %	57.0	54.4	74.7
Mean age, years, M ± m	68.0 ± 12.6	67.5 ± 12.4	66.0 ± 12.5
Labile blood pressure, %	24	26	25.0
Early onset of palpitations or paroxysmal arrhythmias, %	8.5	7.3	5.5
Mean comorbidities count, M ± m	3.60 ± 1.79	3.51 ± 1.86	3.62 ± 2.09
Mean PCI, M ± m	7.55 ± 4.56	7.49 ± 4.74	7.97 ± 4.53

Table 2. **Baseline characteristics of NSTE-ACS subgroups**

Parameter	NSTE-ACS subgroup			Significance for differences between subgroups	
	Non-CAD	Stable CAD	ACS	X^2, P	F, P
Patients count	302	76	219		
Females, %	59.8	64.3	44.2	21.25, < 0.0001	
Mean age, years, M ± m	67.0 ± 12.9	71.0 ± 11.0	67.3 ± 11.9	7.54, 0.0006	
Labile blood pressure, %	35	31	11	37.77, < 0.0001	
Early onset of palpitations or paroxysmal arrhythmias, %	10.9	7.1	3.4	12.96, 0.0004	
Mean comorbidities count, M ± m	3.48 ± 1.79	4.61 ± 2.41	3.36 ± 1.80		3.75; 0.0240
Mean PCI, M ± m	9.33 ± 4.97	8.64 ± 4.85	5.01 ± 3.05		45.88; < 0.0001

Note: Statistical significance (Chi-square, F, P) is given for differences between all 3 NSTE-ACS subgroups.

The latter cohort was divided into 2 subgroups (see table 3), defined on typical or non-typical somatic or medically unexplained physical symptoms [16]:

1. ICD-10 F3x (affective disorders), F4x (neurotic, stress-related and somatoform disorders) and F6x (disorders of adult personality and behaviour) subgroup, n = 107 (82, 22 and 3 patients, respectively).
2. ICD-10 F0x (organic, including symptomatic, mental disorders) and F2x (schizophrenia, schizotypal and delusional disorders) subgroup, n = 128 (112 and 16 patients, respectively).

As the design of the study was retrospective observational, no informed consent needed for inclusion.

Exclusion criteria: in-hospital death, lack of demographic or medical data on personal history and prescribed medications.

The following data were collected and subsequently analyzed:

1. The fact of prescription of psychopharmacotherapy for post-hospital medication.
2. Demographic factors (gender, age).
3. Personal history of CVD and cardiac interventions or surgery.
4. Comorbidities, including potentially psychosomatic diseases.
5. Assessment of anxiety and depression with Hospital Anxiety and depression scale (HADS) [17].
6. Final diagnoses for validation cohort, including comorbidities and conditions associated with high prevalence of affective, cognitive disorders and autonomous dysfunction.
7. For additional cohort, the major symptoms at admission and the final diagnosis were also collected (anxiety, anhedonia, hypochondriasis, delusions, depersonalization, insomnia, sensory hallucinations, cognitive decline).

Statistics were performed with SPSS 23.0 (IBM Inc., USA). We used the descriptive statistics, Kolmogorov — Smirnov test for normal distribution, parametric and non-parametric analyses, i. e. Spearman and Pearson correlations, Mann — Whitney U-criterion. Statistical significance was determined as $P < 0.05$.

Results

Diagnosis of mental comorbidities in cardiology patients

Of 721 patients from the validation cohort, 80 were diagnosed with various mental disorders before admission. 34 patients (4.7 %) were assessed by neurologist, 2 and 1 were consulted by psychiatrist and psychotherapist, respectively. 70 (9.7 %) patients received recommendations do be furtherly observed by neurologist, 12 and 21 by psychiatrist and psychotherapist, respectively. Table 3 represents the symptoms and syndromes found in these patients. Fatigue and cognitive deficiency were the most common findings. 11 participants had medically unexplained chronic pains.

Prognostic meaning of PCI in patients with suspected NSTE-ACS

An additional retrospective analysis was provided for 577 participants who were hospitalized due to suspected NSTE-ACS. During in-hospital assessment, in 302 cases complaints were found to be non-cardiac, 76 were attributed to stable CAD, and in 219 cases initial diagnosis was confirmed (see table 2). Patients from the last subgroup were less likely to be women, to have labile arterial hypertension and early onset of cardiac arrhythmias.

An association between probability of confirmed NSTE-ACS and magnitude of psycho-cardiac comorbidity index (see Figure). The percentage on ruled-out ACS positively correlated with was higher with psycho-cardiac comorbidity index ($r = -0.27$, $p \sim 10^{-10}$).

Table 3. **Prevalence of mental conditions and symptoms in validation group and additional group**

Conditions and symptoms	Prevalence (N, %)	Conditions and symptoms	Prevalence (N, %)
Validation cohort		Additional cohort	
Fatigue	31 (4.3)	Anxiety	196 (82)
Dementia / cognitive deficit	25 (3.5)	Hypochondriasis	66 (27)
Somatoform autonomous dysfunction	18 (2.5)	Mood instability	49 (21)
Anxious disorders	9 (1.2)	Senestopathy	43 (19)
Hypochondriasis	8 (1.1)	Depersonalization	34 (14)
Epilepsy	5 (0.7)	Insomnia	158 (65)
Depression	4 (0.6)	Anhedonia	99 (41)
Other (e. g. delirium, acute psychoses)	12 (1.7)	Cognitive deficit	94 (38)
		Hallucinations	32 (13)
		Delusions	54 (22)

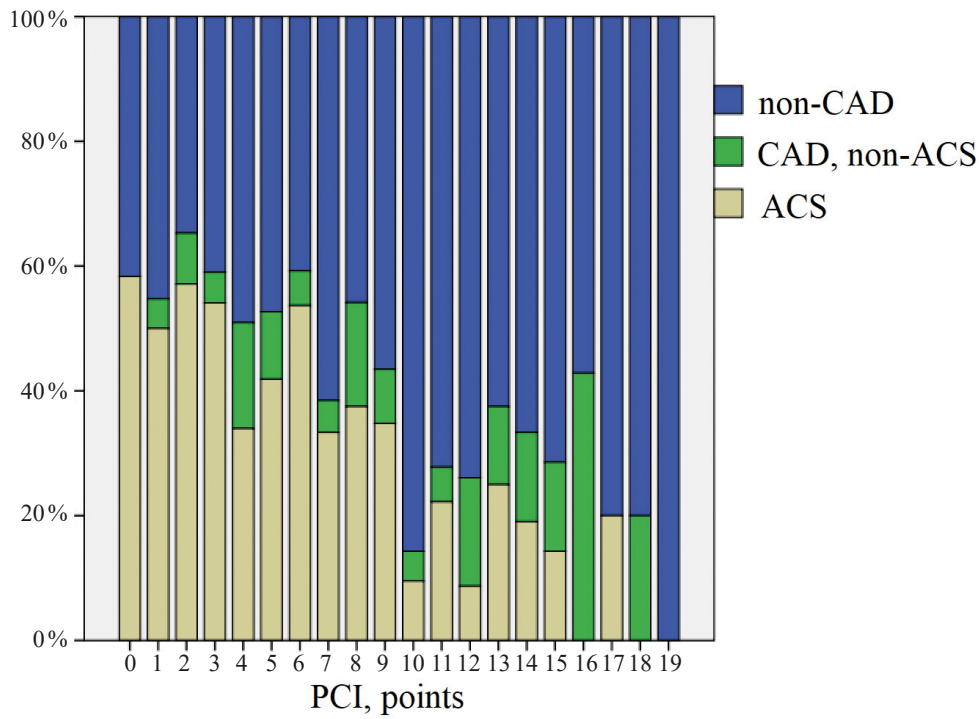

Figure. Percentage of confirmed and excluded NSTE-ACS in patients with different PCI scores

Application of psycho-cardiac comorbidity index to the people with verified mental disorders

The PCI was applied to additional cohort of patients with verified mental disorders. Results demonstrated parallelism between PCI score and separate domains of mental diseases. The spectrum of mental conditions is presented at Table 3.

The mean PCI score on F0x-F2x subgroup was lower compared to F3x-F4x-F6x subgroup (mean score 7.52 ± 4.38 vs. 8.59 ± 4.62 points, respectively, U = 6040.5, p = 0.041). When assessed the association of symptoms with PCI, a negative one was found between delusions and proposed index (8.47 ± 4.45 vs. 6.59 ± 4.48 points, U = 3530.5, p = 0.007). There was a tendency to lower rate of prescription of vasoactive substances in patients with higher PCI (6.55 ± 4.14 vs. 8.26 ± 4.56 points, p = 0.057). Another symptoms and medications demonstrated no association with PCI index.

Psycho-cardiac comorbidity index and Hospital anxiety and depression scale

Of the validation cohort, 231 patients were screened for anxiety and depression with hospital anxiety and depression scale (HADS) (60 % females, mean age 67.6 ± 11.5 years). In 57 cases (24.7 %) the results were incomplete; 168 anxiety subscales and 172 depression subscales were found eligible for further analysis. Of them, 87 scales were collected from patients who presented with suspected NSTE-ACS.

Mean anxiety subscale was 7.58 ± 3.80 points (6.18 ± 3.54 for men and 8.54 ± 3.69 for women, F(1) = 22.25, p = 0.0001); the mean depression subscale was 6.89 ± 3.69 points (5.75 ± 3.81 for men, 7.66 ± 3.43 for women, F(1) = 13.49, p = 0.0002). Distribution or results by clinical groups is presented at Table 4.

Higher PCI positively correlated with higher anxiety (r = 0.26, p < 0.001) and depression HADS subscales (r = 0.17, p = 0.026). Regression coefficient between PCI and anxiety subscale was 0.256 ± 0.082 (i. e. PCI increase at 10 points corresponds to mean HADS-A increase at 2.56 points). The regression coefficient for depression subscale was 0.173 ± 0.088.

Table 4. **Prevalence of anxiety and depression in validation group**

Clinical Group	Men	Women	General subgroup
No anxiety	67.6	43.5	53.3
Subclinical anxiety	19.7	28.7	25
Symptomatic anxiety	12.7	27.8	21.7
No depression	69.0	49.6	56.7
Subclinical depression	24.3	33.0	28.9
Symptomatic depression	6.7	17.4	13.4

Discussion

This study was carried out to assess the prognostic meaning of previously proposed psycho-cardiac comorbidity index for ruling out NSTE-ACS and for screening of mental diseases in general population (firstly, screening of anxiety and depression).

Chest pain is a common symptom of somatoform disorder in general practice. American heart association recommended to screen the patients with CAD for depression in 2008 [10]. Palpitations and chest pain often have non-cardiac origin. Such symptoms may be caused by somatic conditions or medically unexplained. The last group of conditions is responsible for 7 to 17 % of chest pain cases in primary care. It may be misinterpreted as ACS. Various mental conditions (i.e. affective, anxiety, somatoform) are found in over 50 % of emergency cardiac care consumers, especially in cases when no "medically explained symptoms" were found [18]. Due to temporary challenges and impossibility to apply the response forms in long-term, screening for anxiety and depression is complicated [19], forcing to search alternative ways of screening for psycho-cardiac comorbidity. An algorithm proposed in this study is one of such ways.

The most common complaints attributed to mental conditions, according to our study, were fatigue and cognitive deficit. It is contrary to data from other registries showing higher prevalence of anxious and depressive disorders in cardiology patients.

For example, according to S. F. Mujtaba et al. (2020), patients with negative coronary angiography demonstrated 37 % (for males) and 22 % (for females) higher volume of anxiety compared to persons with objectified ACS [20]. According to the same source, the prevalence of anxiety and depression in cardiology population was 10 % and 8 %, respectively [20].

Our study demonstrates gender-specific distribution of anxiety and depression HADS subscales, corresponding to most of the data on this subject.

In general, the data collected during this study, highlight the high significance of mental status in diagnostic algorithms and treatment of patients with cardiac urgent conditions and need for paying special attention to it [6].

The retrospective two-center design of this study is its limitation. Further validation of proposed index on other medical groups is needed (firstly, in pulmonology and gastroenterology departments, were burden of psychosomatic disorders is high).

As alexithymia is known to contribute to clinical presentation of psychosomatic disorders, this aspect should be also evaluated in context of screening for mental conditions in general practice. Another factor that should not be neglected is a variable nociceptive threshold in patients with labile blood pressure (which might be triggered by chronic pain). Further prospective randomized trials are needed to estimate contribution of these factors into course of cardiac diseases.

Conclusions

The proposed Psycho-cardiac comorbidity index is a valid additional diagnostic tool to rule-out the non-ST-elevation ACS, representing the anxious and depressive symptoms in cardiac in-hospital patients.

The found social, demographic and neurological profiles of high-PCI patients correspond to ones found in patients with verified affective, somatoform and psychogenic

disorders. These patients need interdisciplinary approach and initiation of psychopharmacotherapy should be considered.

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Received: May 17, 2021
Accepted: September 17, 2021

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CARDIAC SURGERY

UDC 616.132-007.64

CT-fusion-guided thoracic endovascular aortic repair: Case report and literature review

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For citation: Khilchuk A. A., Payvin A. A., Scherbak S. G., Guryev V. V., Karmazanashvili E. G., Lazakovich D. N. CT-fusion-guided thoracic endovascular aortic repair: Case report and literature review. *Vestnik of Saint Petersburg University. Medicine*, 2021, vol. 16, issue 3, pp. 180–189.
https://doi.org/10.21638/spbu11.2021.305

Interventional and hybrid methods of treatment, combining open surgical and endovascular repairs, are the most promising areas in the surgery of the thoracoabdominal aorta. Recent studies, however, have demonstrated that complex thoracic endovascular aneurysm repair (TEVAR) is one of the most high-dose endovascular interventions. In addition, TEVAR is associated with the use of a significant volume of contrast media (CM), which can lead to contrast-induced acute kidney injury (CI-AKI). The use of advanced imaging techniques and computed tomographic fusion (CT-fusion) in routine practice can potentially reduce operation duration, radiation exposure and CM volume usage. We analyzed the literature on CT-fusion in endovascular aortic repair and present a clinical case of a 50-year-old male with a history of concomitant blunt chest trauma. CT of the chest revealed an aneurysm of the arch and descending aorta after traumatic dissection of the aorta (IIIa DeBakey, type B Stanford), post-traumatic diaphragmatic hernia of the left dome of the diaphragm with stomach and intestinal loops prolapse. The patient underwent a staged hybrid intervention — subtotal aortic arch debranching followed by CT-fusion-guided semi-arch TEVAR. CT-fusion is a dynamically developing technology, may reduce the CM volume, the duration of the procedure and radiation exposure and requires further research.

Keywords: aorta, endovascular aortic repair, aortic aneurysm, computed tomography, CT-fusion.

Introduction

Despite the rapid development of noninvasive imaging methods, thoracic aortic aneurysms and dissections remain one of the most frequent causes of sudden cardiac death, amounting to 5.9 cases per 100K people per year [1]. Aortic dissection is a violation of the integrity of its intimal and medial layers, resulting in intimal detachment and intramural hematoma. In the natural course of dissection, inflammatory response to thrombosis in the medial layer initiates further necrosis and apoptosis of aortic smooth muscle cells and elastoid degeneration, which may cause aortic aneurysm and aortic wall rupture [2]. Based on the area of proximal fenestra dissection, there are several classifications. The most common today are the DeBakey and Stanford classification systems.

According to the DeBakey classification, there are 3 types: Type I, when dissection involves the aortic arch, the ascending and descending parts of the thoracic aorta; Type II — proximal fenestration and dissection involve only the ascending aorta; Type III — proximal intimal tear is limited only to the descending thoracic aorta. Since the treatment tactics of Types I and II are similar, currently the most common anatomical classification is Stanford, according to which Type A is the proximal/ascending type, and Type B is the distal/descending one [3].

For planning various types of endovascular repair for aortic dissection, Mitchell et al. have developed a special anatomical classification based on which the aortic arch, its ascending and descending sections are divided into zones within which proximal stent-graft is fixed (Fig. 1) [4].

According to Coady et al., about 20 % of thoracic aortic aneurysms are associated with congenital connective tissue defect, the most famous of which are the Marfan, Ehlers-Danlos syndromes and some others [5]. Acquired aneurysms can be caused by aortic arterial sclerotic disease, infections (syphilitic mesaortitis, "mycotic" aneurysms), autoimmune diseases (Takayasu, Behcet's, Ormond's diseases), iatrogenic aortic lesions, and injuries, etc. [6; 7]. Traumatic aortic injury, both independently and with subsequent aneurysm formation, in the absence of diagnosis and treatment can be fatal in 80 % [7]. 75 % of thoracic aortic traumatic injuries are the result of road traffic accidents. The mechanism is based on the abrupt displacement of the heart and aortic arch relative to the fixed aortic ligament of the descending aorta [6]. Due to the lack of specific symptoms, the patient's condition is often underestimated at presentation. The optimal medical therapy of descending aortic dissection alone may lead to significant dilatation, which further requires repair. One of the risk factors of aneurysm rupture is growth rate. The average growth rate of non-traumatic thoracic aortic an-

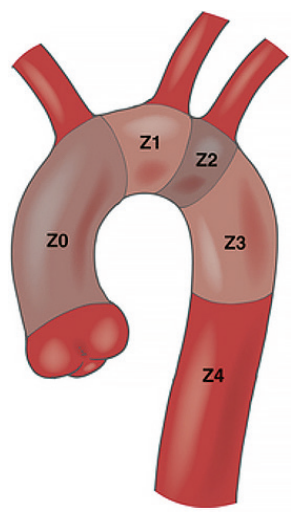

Fig. 1. Mitchell — Ishimaru graft fixation zones

Z0 — from ascending aorta to brachiocephalic trunk; Z1 — from brachiocephalic trunk to LCC artery; Z2 — from LCC artery to LSA; Z3 — from LSA to descending thoracic aorta; Z4 — to inferior thoracic aorta

Note: LCC artery — left common carotid artery; LSA — left subclavian artery.

eurysms is 0.1 cm/year, while the average growth rate of thoracic aortic aneurysms with chronic dissection is from 0.24 cm/year for small aneurysms (over 4.0 cm) to 0.48 cm/year for aneurysms over 8.0 cm in diameter [8].

Computed tomography (CT), transesophageal echocardiography and magnetic resonance imaging (MRI) are most used for the diagnosis of thoracic aortic aneurysm [9; 10]. Transthoracic echo in parasternal position enables to visualize well only the root and proximal part of the ascending aorta, so it is a low sensitive diagnostic method, in contrast to transesophageal echo, especially if the aneurysm is localized in the descending aorta [11]. CT-angiography is the fastest, noninvasive most sensitive, specific, and accessible diagnostic method providing all necessary anatomical information for planning aortic repair. CT advantages are the capability of detailed assessment of anatomy and damage type, aneurysm localization, its relationship with main branches, intimal fenestration, etc. In case of contraindications to CT-angiography, such as CM intolerance, chronic kidney disease (CKD) C3b-C4, an alternative diagnostic method is MRI. Noninvasive imaging methods allow to determine patient management tactics and preferred surgical treatment method.

The most developing and promising trend of thoracoabdominal aortic aneurysm surgery is interventional and hybrid treatment methods characterized by a combination of open surgical and endovascular aortic intervention in one procedure or two different steps. These techniques can be an alternative to standard, technically challenging open surgical interventions associated with a high risk of postoperative complications and mortality. Most authors now distinguish 3 types of hybrid interventions on aortic arch aneurysms, depending on the anatomy and presence of graft fixation zones. In case of isolated arch aneurysm, classical debranching is performed, which is basically the ligation of the aortic branch ostia and switching blood flow to the main branches on a multibranch prosthesis. Depending on proximal fenestration location, debranching can be total — when all the branches of aortic arch are switched, subtotal — when blood flow is switched along 2 or more vessels, and partial — when one vessel is switched. The second stage of intervention is single-step or delayed stent-graft implantation. Preliminary debranching allows to avoid complications in the postoperative period. According to recent publications, even with partial blocking of aortic arch branches with an endoprosthesis, the hospital risk of stroke is 8 %, while the incidence of perioperative strokes does not exceed 2 % when the brachiocephalic arteries are switched [12; 13]. In case of proximal fenestration in the ascending aorta, the 2nd type of hybrid interventions is performed — creating an adequate proximal fixation zone using the open prosthesis of the ascending aorta [14]. In extended aneurysms (mega-aortic syndrome), when both the proximal and distal graft attachment zones are missing, the 3rd type of hybrid surgery is performed — the total open repair of the ascending aorta and arch in elephant trunk modification (Borst procedure), followed by stent-graft implantation into the thoracic aorta, which is fixed with transition to the overlying prosthetic aortic part [15–17].

When performing thoracic endovascular aortic repair (TEVAR), the morphology of the proximal and distal landing zones as well as aortic size should be well examined. For the intraoperative visualization of the anatomy and orientation of the endovascular instrument, it is reasonable to use auxiliary methods of imaging. CT-fusion is a method that allows projecting a 3D-anatomical model with color markers onto a live fluoroscopic image. Data overlay aligns images with anatomical landmarks, bony or vascular, and merges

data with live fluoroscopy into a single coordinate system. The resulting CT mask automatically adapts to changes in C-arm angle, table position, and field of view. The CT mask with planning markers and lines is available throughout the operation and can be further adjusted to changing anatomy. Although the clear benefit of using CT-fusion in routine endovascular aortic repair (EVAR) and TEVAR has not yet been demonstrated, the technology allows to significantly reduce the amount of the injected CM and procedural time in advanced aortic interventions (ChEVAR, BEVAR, FEVAR) [12].

Case presentation

Patient K., 50-years-old, with a long-term course of arterial hypertension. In 2009 he was treated for the consequences of a traffic accident (a blunt thoracic and abdominal trauma). 2010 CT data show a transection in the thoracic aorta and a left hemidiaphragm defect. He has refused to undergo surgical intervention.

Upon re-examination, native CT and CT-angiography visualized posttraumatic left hemidiaphragm hernia with prolapsing large and small intestine loops, significant left lung collapse, and the postdissection aneurysm of the aortic arch and descending section of type IIIa, according to DeBakey classification, Stanford type B (Fig. 2).

The absence of an adequate proximal graft fixation zone to preserve the left common carotid (LCC) and left subclavian artery (LSA) ostia did not allow isolated TEVAR. Despite the relative safety of endograft LSA overlay, the subsequent annual risk of ischemic stroke in the posterior cerebral circulation is up to 15 % according to various authors [13]. Aggressive positioning with overlaying the left CCA mouth also significantly increases stroke risk both intra- and postoperatively. Given the relatively young age and therefore significant life expectancy, the absence of severe somatic pathology, it was decided to abandon parallel graft techniques, in-situ fenestration for LCC and LSA or for LSA, and 1 parallel LCC artery graft. Ex consilium together with cardiothoracic surgeons, it was decided to perform the subtotal 1st-stage debranching of the aortic arch followed by endovascular repair with 1 stent-graft from the Z1 zone (Figure 1).

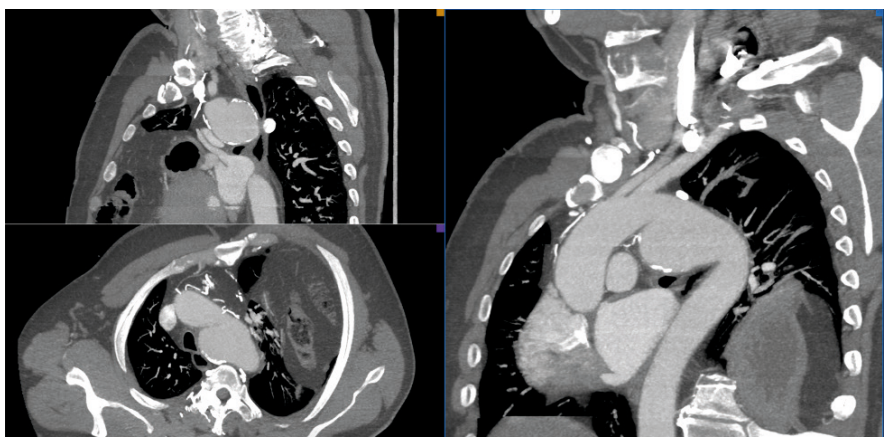

Fig. 2. Thoracic aortic aneurysm at the isthmus area (indicated by arrows), the outcome of DeBakey type IIIa traumatic dissection. The maximal diameter is 68 mm

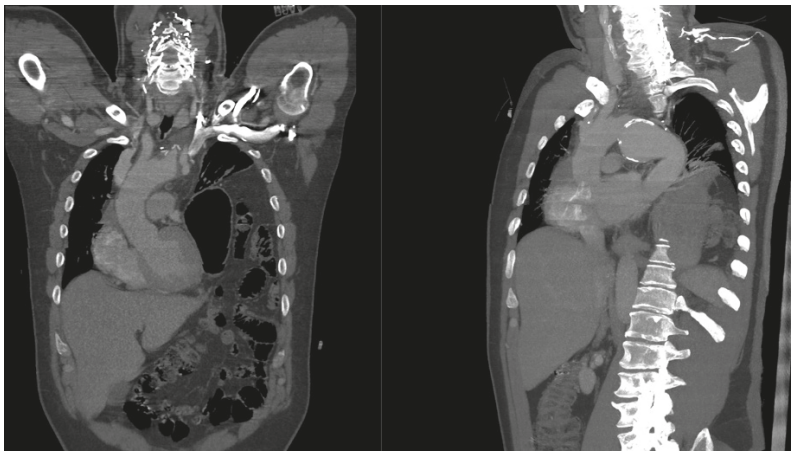

Fig. 3. Condition after subtotal LCC artery and LSA debranching. Left: arrows indicate prosthetic branches to the LCC artery and LSA. Right: arrows indicate the clipped native LCC artery and LSA with the formation of the proximal endograft fixation zone

Under the conditions of artificial blood circulation (ABC) and antegrade cerebral perfusion combined with systemic hypothermia, under cerebral oximetry control, LSA and LCC artery debranching was performed using a trifurcated arch prosthesis with an additional perfusion branch. The 1st stage was complicated by class 3a CKD (CKD-EPI GFR at 52 mL/min/1.73m^2) according to KDIGO 2012 [28]. Seven days after debranching and adequate oral and intravenous hydration, thoracic aortic CT-angiography was performed: LCC artery and LSA debranching visualized, a thoracic aortic aneurysm was visualized as an outcome of DeBakey type IIIa dissection, Stanford type B (Fig. 3). Unfortunately, the radiologists' fear of provoking contrast-induced acute kidney injury (CI-AKI) resulted in a smaller contrast medium volume and, consequently, a lower quality of CT-angiography, yet the necessary 3D information was obtained.

Eight days later, the endovascular repair of the arch and descending aorta was performed. Preoperative spiral CT-angiography data after debranching using the EVAR ASSIST software suite (GE Healthcare, France) had been previously converted into 3D-reconstruction on the Advantage Workstation VolumeShare 4.7 (GE Healthcare, France) and combined with fluoroscopy in real time (Figure 4). The entire CT mask setup was performed by the first operator intraoperatively without any additional staff. The obtained 3D-reconstruction of the thoracic aorta with color markers at brachiocephalic trunk ostium was used during the surgery as a navigation map over fluoroscopy. The right common femoral artery (CFA) was punctured under ultrasound (US) control, a 6F introducer (Terumo, Tokyo, Japan) was inserted into the arterial lumen, 2 sutures were created using Perclose ProGlide (Abbott, USA) suturing device. Additionally, through the right radial artery PigTail 5F (Cordis, USA) catheter was inserted and positioned in the ascending aorta. The right femoral artery introducer was replaced with a 12F (Boston Scientific, USA) and an ultra-hard Lunderquist (Cook Medical, USA) guidewire was inserted into the ascending aorta. An endograft Valiant Captivia VAMF3434C200TE (Medtronic, Minneapolis, USA) was positioned at Z1 zone and opened under CT-fusion control (Fig. 4).

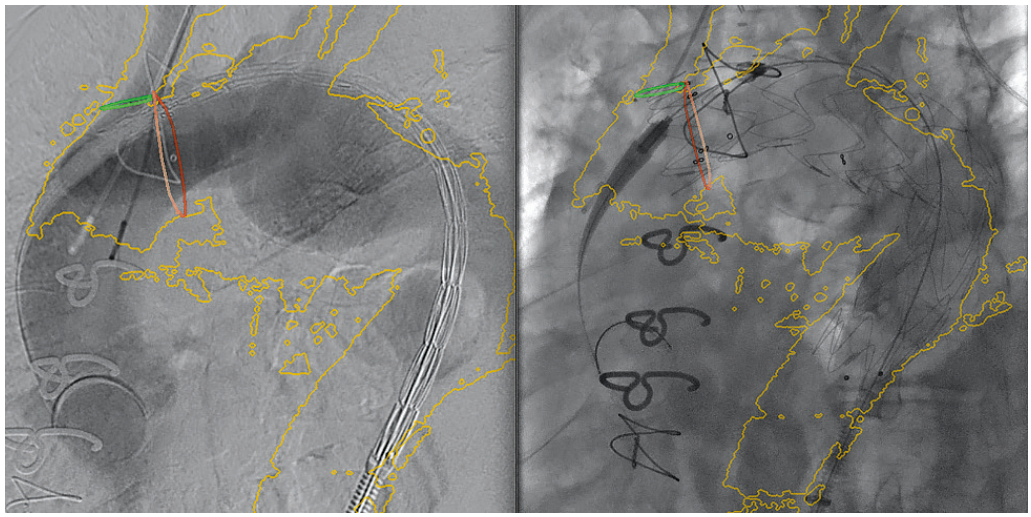

Fig. 4. Endovascular repair from Z1 zone using CT-fusion technique. Left: arrow indicates distal edge of covered endograft part, positioning by color markers of CT-model. Right: arrow indicates opened endograft in Z1 zone with coronal fixation at brachiocephalic trunk level

The control angiography showed no signs of graft malposition or visible endoleak, the aneurysm was excluded from blood flow (Fig. 5). The puncture site of the right CFA was sutured percutaneously. The operation took 45 minutes, the patient's effective dose was 3.5 mSv, the CM volume was 65 ml. The fusion of the 3D thoracic aortic model with live fluoroscopy allowed to significantly reduce the patient dose, reduce CM usage, and almost completely focus on CT-fusion during implantation.

In the early postoperative period, the patient was dynamically examined by an intensive care physician and a neurologist to control the possible early development of paraplegia. The patient's neurologic status remained unchanged after endovascular repair. Aspirin

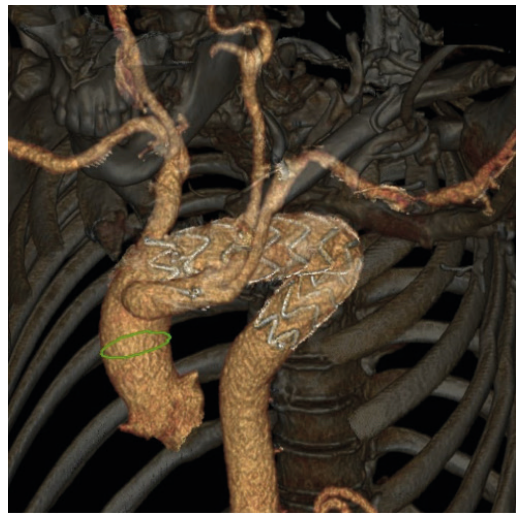

Fig. 5. Control CT-angiography after 3 months. Endograft position (indicated by arrow) from Z1 zone. Aneurysm off blood flow, no leakage and dSINE detected. LCC artery, LSA anastomoses with no signs of stenosing

Note: dSINE, distal stent-graft-induced new entry.

monotherapy was prescribed, and CT-angiography was recommended in 1 month, with monitoring serum creatinine (SCr).

After 3 months, according to CT-angiography, the aneurysm was completely excluded from the blood flow, no endoleak or new stent-induced dissections were detected. LCC artery and LSA anastomoses had no signs of stenosing. As of writing this, the patient was in good health, had no complaints, led an active lifestyle, and had been under observation for over 10 months.

Discussion

To date, the ESC guidelines for aortic disease treatment make the decision to perform TEVAR according to anatomy, pathology, comorbidities, expected life span, using multidisciplinary approach [18]. The advantage of endovascular interventions is their low injury rate and a significant reduction in patient rehabilitation periods. However, in large aneurysm interventions with fenestrations more proximal to the LSA, one-stage graft implantation is still complex or involves moderate to high surgical risks. Total or subtotal brachiocephalic arteries debranching as the first step allows to form a site for further TEVAR especially in young patients. Marullo et al., in a series of studies of patients with DeBakey type I aortic dissection who underwent ascending and aortic arch repair with debranching and subsequent endovascular treatment, showed that hospital mortality was 4.2 %, with 2-year survival rate at 92.1 ± 7.9 % [19].

Due to growing interest in hybrid therapies, high usage of CM and exposure of both patients and staff remain an important issue. Based on data from several large meta-analyses, imaging and image fusion programs during the TAE procedure have been shown to reduce both CM amount and radiation dose. Hertault et al. have demonstrated a significant decrease in CM amount injected and a trend to reduce the time of surgical intervention and fluoroscopy [20]. However, procedure time may depend on many factors, such as operator experience or perioperative complications [20]. For example, in 2011, Kobeiter et al. reported the first case of endovascular reconstruction of the thoracic aorta using an image fusion technique without CM use, meanwhile noting a sharp increase in fluoroscopy time [21]. Yet in a study by McNally et al., procedure time (from skin incision/puncture to dressing) was a major factor. According to the data presented, there was a significant reduction in radiation exposure (3.4 ± 1.9 vs. 1.38 ± 0.52 mGy; P = 0.001), fluoroscopy time (63 ± 29 vs. 41 ± 11 min; P = 0.02) and CM use (69 ± 16 vs. 26 ± 8 ml; P = 0.0002) when using intraoperative 3D-fusion CT [22].

Although the above data suggest that image fusion can reduce 2 key parameters (radiation dose and contrast volume), this technique is still relatively new. Information projected on the fluoroscopic screen is extracted from a preoperative CT scan that was performed at a different time, on a different table, and with the patient in a slightly different position. A combination of these factors can affect the accuracy of the superimposed image. In addition, accuracy may be adversely affected by anatomy distortion by endovascular devices and patient movements including breathing. Tortuous vessels can be straightened by the insertion of rigid endovascular guidewires.

Recent studies describing image fusion experience show that the CT-fusion method is not accurate enough to rely on completely [23–27]. However, despite possible inaccuracies, the image overlay technique can serve as a rough guide for the physician.

Another disadvantage of the Fusion-Imaging technology is the additional need to purchase a software suite. Moreover, the learning curve can affect fusion technique accuracy. The time taken to fuse images and fusion inaccuracies are expected to be reduced as experience increases. However, to date, there are no studies reporting any effect of the learning curve on 3D image fusion technology.

Conclusions

1. Combining 3D CT imaging with fluoroscopy is a dynamically developing technology, and to date its potential has not been fully unlocked.
2. Our clinical case and literature data suggest that the use of this technique significantly reduces CM amount injected and reduces intervention duration and fluoroscopy time.
3. The high complexity of current interventions requires the use of auxiliary techniques to combine 3D-imaging and fluoroscopy for planning and intraoperative positioning of endoprostheses. However, due to the software's complexity and high cost, this technology is still not widespread.
4. The disadvantages of this technology include the fact that the 3D model remains rigid and immobile. After all, even small changes in patient position, pronounced respiratory excursion can lead to errors in stent-graft positioning. Moreover, the anatomy of the aorta and its branches may change if rigid guidewires, catheters or endoprostheses are inserted, which requires recalibrating the 3D-model.
5. The prospect of this technique is also revealed for other interventions, such as transcatheter aortic valve replacement, atherosclerotic lesions of lower limb arteries, embolization in interventional oncology and embolization using spirals and adhesive compositions in neurosurgery.

Our center's experience has shown that the fusion of 3D images derived from CT data can facilitate intraoperative management during aortic endovascular repair, as well as significantly reduce CM amount used and reduce operation time. Drawn rings and color markers are useful for visualization, overlay correction, and manipulation control. There is a need for further development and refinement of the technique to ensure accurate, real-time automatic registration and correction of the CT mask according to the changed vascular anatomy after rigid instrument insertion.

The authors would like to express their gratitude to S. V. Vlasenko, Head of the Interventional Department, St. Petersburg State City Hospital no. 40, for his assistance in preparing this publication.

Anton A. Khilchuk provides consulting services to GE Healthcare LCC, while the other authors declare no conflicts of interest related to this publication.

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Received: June 7, 2021
Accepted: September 28, 2021

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PATHOLOGICAL PHYSIOLOGY

UDC 57.053

Purinergic regulation: From a risky hypothesis to a triumphant theory

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For citation: Kamran Sarkandi M., Serebryanaya N. B. Purinergic regulation: From a risky hypothesis to a triumphant theory. *Vestnik of Saint Petersburg University. Medicine*, 2021, vol. 16, issue 3, pp. 190–202. https://doi.org/10.21638/spbu11.2021.306

With the discovery of the ATP structure in 1929, significant progress was made in understanding the role of nucleosides and nucleotides in the body. One of the most important breakthroughs is associated with the determination of the function of an autacoid in ATP, a participant in purinergic signal transmission. For the first time, this function of ATP was pointed out by Professor Geoffrey Burnstock in 1972. Purinergic signaling activators are extracellular nucleotides including ATP, ADP, UTP, UDP, and adenosine nucleoside. The purinergic signaling pathway begins with the synthesis and intracellular accumulation of nucleotides, and then their release from the cell under various physiological and pathological conditions. In the extracellular spaces, nucleotides are hydrolyzed by various enzymes with the removal of phosphate groups, which leads to the appearance of various regulatory molecules that interact with P1 and P2 purinergic receptors. This ligand-receptor interaction changes the functional state of the target cell. In turn, the expression of purinergic receptors changes depending on the functional state of the cell. The participation of purinergic regulation in the development of many diseases indicates that by changing the concentration of signaling molecules, it is possible to change the course of pathological processes, in particular the activity of inflammation and the direction of immune responses. This article provides a brief review of the literature on the structure of nucleotide and nucleoside autacoids, enzymes involved in their metabolism, specific purinergic receptors.

Keywords: purinergic signaling pathway, Adenosine, ATP, Purinergic regulation, P1 and P2 receptors.

Introduction

The discovery of ATP in 1929 was first reported by 2 groups of researchers, Karl Lohmann [1] from Germany and Cyrus Hartwell Fiske, and Yellapragada Subbarow [2] from the USA. In the same year, Alan Drury and Albert Szent-Györgyi discovered that adenosine nucleoside and adenylic acid (adenosine 5'-monophosphate, 5'-AMP) act as signaling molecules in the cardiovascular system [3]. However, a more complete understanding of the adenosine-5′-triphosphoric acid (ATP) regulatory role and the creation of the concept of purinergic signaling pathway is associated with the Jeffrey Bernstock's research. In the 1960s, as a young researcher, he studied autonomic neurotransmission in which two main transmitters (acetylcholine and noradrenaline) were not involved [4]. The term purinergic signaling pathway was first time used by Burnstock in an article of Pharmacological Reviews in 1972 [5]. He suggested that stimulation of any nerves releases a whole "cocktail" of biologically active substances, transmitters, and modulators can significantly affect the effectiveness of the main transmitter. The idea of co-transmission was not accepted by the scientific community for a long time, since the scientific authority of the Nobel Prize laureate Henry Dale, who argued (Dale's principle) that each neuron emits only one type of neurotransmitter [6], was incomparably higher than that of Professor Burnstock who was not widely known in the scientific community. His other hypothesis was even more revolutionary. According to this hypothesis, there are also some "noncholinergic, nonadrenergic" nerves in the autonomic nervous system aside from cholinergic and adrenergic nerves, and the effects of which are not mediated by classical mediators, acetylcholine, and noradrenaline. After doing a lot of experiments and analysis, Burnstock suggested that purine compounds, such as adenosine and adenosine-5′-triphosphoric acid (ATP), serve as mediators in these nerves, and therefore, he called them purinergic nerves [7]. However, since both of these purines are widespread in the body and are present in absolutely all cells, it was difficult to imagine their role as specific signaling molecules in the nervous system. It was objected to Bernstock that ATP cannot be an intermediary due to its widespread occurrence, molecule instability, and high molecular electric charge. Although the extracellular hydrolysis of ATP in tissue was demonstrated as early as the 1930s, the analysis of these processes required the development of more advanced biochemical methods, which became available decades later. Important discoveries of the early 1990s confirmed the existence of the purinergic signaling pathway. The first G protein-coupled receptor (GPCR) for ATP (P2Y1 receptor) was cloned by Burnstock and Julius in 1993. The purinergic hypothesis shortly became one of the most hotly debated topics in neurophysiology and neuropharmacology [8].

The model developed by Bernstock for the synthesis, release, storage, and inactivation of ATP at the purinergic neuromuscular junction is still relevant. Per this model, ATP is released by various cells, and this process is significantly enhanced under conditions of cellular stress or damage. Further, ATP is rapidly converted to adenosine by the enzymes ectonucleotidases. The original term ecto-ATPase (1955), ectoenzyme and ecto-apyrase were used at the International Symposium on Enzyme Chemistry in 1957 by Wladimir A. Engelhardt and Tatjana Wenkstern [9]. The main stages of the study of the purinergic system are shown in figure 1. In this review, we present the structures of nucleotide and nucleoside mediators, the types of enzymes involved in their metabolism, and specific purinergic receptors.

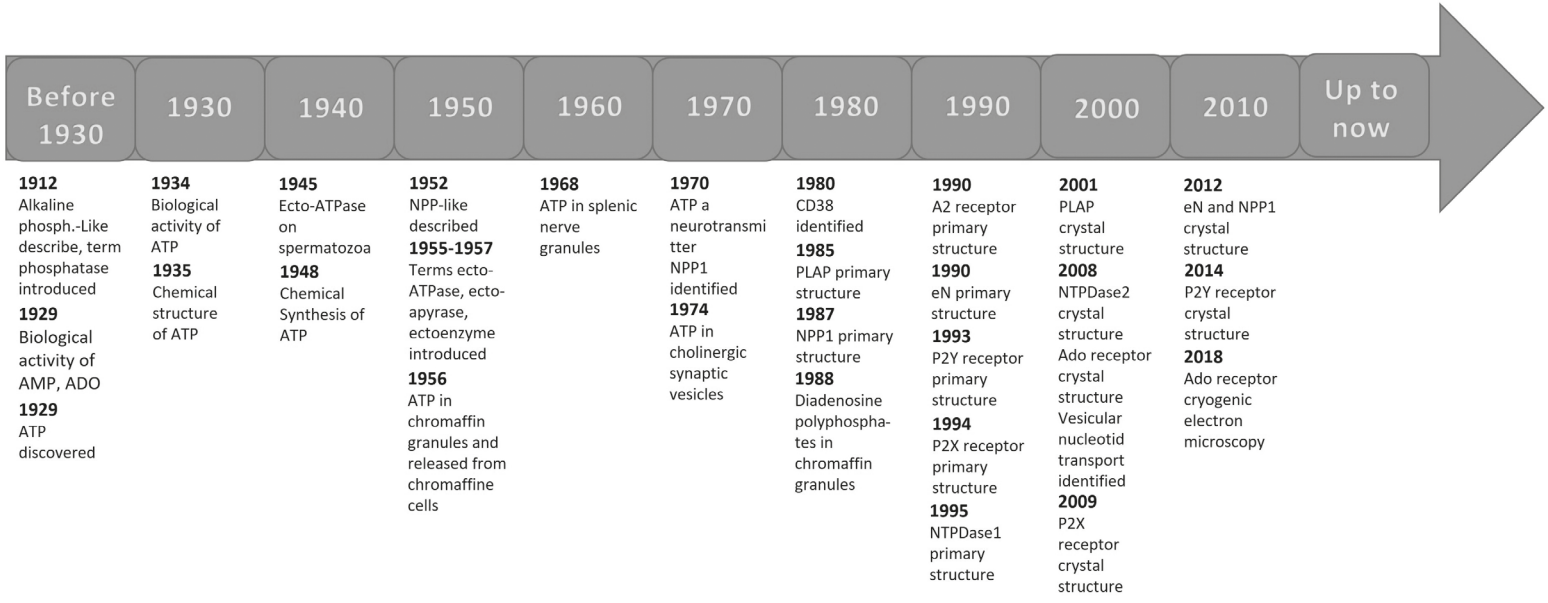

Fig. 1. A brief history of the purinergic signaling pathway discovery (adapted from [10]). In the 1980s the first efforts were made to purify ectoenzymes of this pathway. For the first time, ATP diphosphohydrolase was purified to homogeneity from the human placenta in 1995. In addition, in 1996 the apyrase enzyme that catalyzes the hydrolysis of ATP to yield AMP and inorganic phosphate (Pi) was cloned from potato tubers and was demonstrated to be related to CD39. Then a single mammalian ecto-apyrase was sequenced and expressed in 1997. Later it was demonstrated that this enzyme preferentially hydrolyzes ATP and appeared to function as an ecto-ATPase rather than an ecto-apyrase. In 1998, the identification of four paralog enzymes in the human displayed that an entire gene and protein family must exist. Now eight paralogs are encoded in the mammalian genome

Extracellular nucleotides and nucleosides

Nucleotides and nucleosides are ubiquitous molecules that are involved in many cellular processes such as the formation of nucleic acids, energy intermediates, allosteric modulators, coenzymes, and signaling. Almost all cells secrete nucleosides and nucleotides in various physiological and pathological conditions, such as cellular stress, infections, inflammation, pain, and cancer. Under normal conditions, ATP and other nucleotides are found in the extracellular space in the nanomolar concentration. But in the intracellular space, their concentration is much higher, from 5 to 10 mmol/L [11]. The peculiarities of nucleotides are hydrophilicity and rapid hydrolysis in the extracellular space.

Adenosine formed after enzymatic dephosphorylation of ATP can transport across cell membranes by the special carrier proteins [12]. Adenosine has a multidirectional effect on cells [13; 14]. With an increase in extracellular concentration, adenosine can dump the immune response, as it amplifies the signal from certain immune mediators that suppress the activity of immune cells. This situation is observed in chronic inflammation or malignant tumors [15]. Taking into account the possibilities of purinergic regulation, therapeutic agents that can affect the components of this system in various diseases are being developed.

The interaction of nucleotides and nucleosides with two main groups of purinergic receptors (P1 and P2) on cell membranes [16] determines the activity of neurons, glia, platelets, as well as various types of cells of the cardiovascular, immune, endocrine, gastrointestinal and other systems [11; 17].

Enzymes involved in the purinergic pathway

The degradation of nucleotides and nucleosides is mediated by a wide range of enzymes, some of which are shown in figure 2.

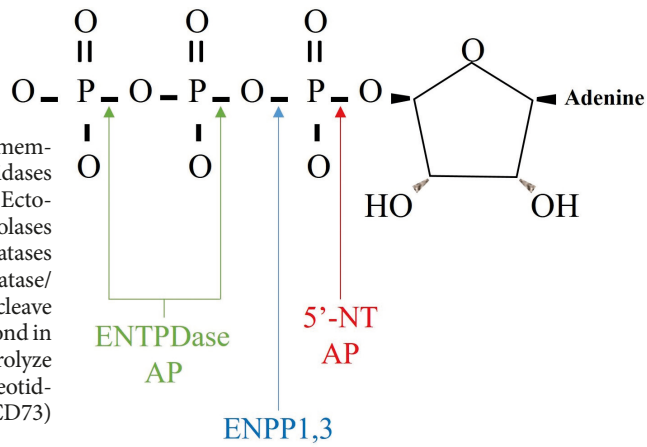

Fig. 2. Different cleavage sites of members of the four types of ectonucleotidases on extracellular ATP, ADP, and AMP. Ecto-nucleoside triphosphate diphosphohydrolases (ENTPDases, CD39), alkaline phosphatases (APs), and ecto-nucleotide pyrophosphatase/phosphodiesterases (ENPPs) 1 and 3 cleave ATP and ADP. ENPPs cleave the same bond in ATP and ADP whereas ENTPDases hydrolyze different bonds. Eventually, ecto-5′ nucleotidase (5′-NT) and APs hydrolyze AMP (CD73) (adapted from [11])

Ecto-nucleoside triphosphate diphosphohydrolases (E-NTPDases). E-NTPDases (CD39 family) are the most important nucleotide-hydrolyzing enzymes involved in purinergic signaling. They catalyze the hydrolysis of the γ and β-phosphate residues of triphosphonucleosides (ATP, UTP), and diphosphonucleosides (ADP, UDP). NTPDases

are involved in various aspects of adenosine receptor signaling, including termination of P2 receptor activation, protection of sensitive P2 receptors from desensitization, and enhancement of some receptor activation [18].

Four members of NTPDases including NTPDase1/CD39, NTPDase2/CD39L, NTPDase3/CD39L3, and NTPDase8 are located at the cell surface and the NTPDase5 and NTPDase6 are in secretory form. Membrane-bound NTPDase1 (NTPDase1/CD39) hydrolyzes ATP almost directly to AMP with the temporary formation of small amounts of free ADP [19]. In contrast, NTPDase2, upon hydrolysis of ATP, releases mainly ADP, an agonist for nucleoside diphosphate-sensitive receptors such as platelet receptors P2Y1 and P2Y12 [20]. Further, ADP is slowly dephosphorylated to AMP by ecto-5'-nucleotidase (Ecto5'NTase/CD73). NTPD1 is expressed on natural killer cells (NK), dendritic cells (DC), monocytes, and subpopulations of activated T cells [21; 22]. This enzyme plays an important role in the creation of regulatory nucleotides that regulate neutrophil chemotaxis and inflammatory activity [21].

Ecto-nucleotide phosphodiesterase/pyrophosphatases (E-NPPs). In this enzyme family, there are seven members include ENPP1 to 7. They can hydrolyze ATP to AMP but not to adenosine because their cleavage sites are different from ENTPDase (Figure 2). ENPP1, 2, and 3 hydrolyze pyrophosphate or phosphodiester bonds in ATP and ADP, nicotinamide adenine dinucleotide (NAD^+), flavin adenine dinucleotide (FAD), and possibly also cyclic AMP (cAMP). These enzymes are expressed on epithelial surfaces of respiratory epithelium, liver epithelium, kidney epithelium, and intestinal epithelium [23].

ENPP1 (CD203a) can hydrolyze both NAD^+ and adenosine diphosphate ribose (ADPR) to AMP. ADPR is produced by cyclic ADP ribose hydrolase (CD38), and further, it is processed by CD203a into AMP. The CD38-CD203a enzyme axis, operating independently or in synergy with the CD39/CD73 pathway, and contributes to the generation of the adenosine [24]. ENPP1 hydrolyzes extracellular ATP to form inorganic pyrophosphates (PPi), which are involved in bone mineralization, the calcification of vascular smooth muscle cells, and other tissues during inflammation [25]. ENPP1 is expressed in several immune cells and also is involved in changing the phenotype of macrophages from M1 to M2. As a result, inhibition of ENPP1 may provide immune regulation in the treatment of cancers and pathogenic infections like tuberculosis [26].

ENPP1, 3, 6, and 7 can also hydrolyze phospholipids which are singled out by lysophospholipase D (lysoPLD), this process is associated with the production of the bioactive lysophosphatidic acid (LPA) from lysophosphatidylcholine (LPC) [27].

Ecto-5′-nucleotidase (5′-NT). 5′-nucleotidase (CD73) is an enzyme that produces adenosine from AMP. CD73 has enzymatic function as a nucleotidase and non-enzymatic function as an adhesive molecule that can regulate cell interaction with extracellular matrix components [28]. 5′-NT is expressed by several types of cells such as stromal cells, follicular dendritic cells, endothelial cells, regulatory T cells (Treg), B lymphocytes, and many tumor cells. Under conditions of hypoxia and the action of inflammatory mediators, the activity of this enzyme is significantly increased [29; 30]. Lung cells, including the epithelium, vascular endothelium, or immune cells, express high levels of CD73 and can provide high production of extracellular adenosine during acute lung injury [31]. The activity of 5′-NT also rises as the concentration of adenosine increases. 5′-NT is upregulated in neutrophils, monocytes, and macrophages which is paralleled by enhanced expression of A2A receptors in them. Modulation of 5'-NT activity allows the conversion of inactive

precursors of the A2A receptor agonist into an active anti-inflammatory form at the sites of inflammation [32].

Alkaline phosphatases (APs). Alkaline phosphatases (APs) are a family of endogenous metalloenzymes that are present in various organs and blood serum [33]. AP has hydrolytic phosphatase and transphosphorylase activity targeting a variety of molecules [34].

AP is involved in immune responses to tissue damage and inflammation in many diseases [35; 36]. This enzyme binds to immunoglobulins in the blood and with an increase in the concentration of immunoglobulins, its activity also increases. The increased activity of serum AP in many inflammatory conditions can be used as a protective agent to reduce systemic inflammation. There is a strong positive correlation between AP activity and adenosine production [37]. It was shown that AP may be the main soluble blood ectonucleotidase in the setting of cardiopulmonary bypass surgery [38].

Adenosine deaminase (ADA). Adenosine deaminase (ADA) is one of the most important enzymes involved in the conversion of adenosine to inosine. Inosine has immunomodulatory, cardioprotective, and cytoprotective effects [39; 40]. ADA isoforms in humans include ADA-1, -2, -3. ADA-1 may exist either as low molecular weight or as a high molecular complex with the ADA-binding enzyme dipeptidyl-peptidase IV (CD26) or the adenosine receptor subtypes A1 and A2B [41]. Besides taking part in adenosine catabolism, ADA-1 may interact with cell surface anchoring proteins, acting as an ectoenzyme. ADA-1 can be expressed in different tissues and cells like the thymus, spleen, intestine, dendritic cells, and lymphocytes [11; 42; 43]. In pathological conditions such as inflammation, myocardial ischemic injury, leukemia, and lymphomas, this enzyme is a suitable drug target for their management [44; 45].

ADA-2 displays high similarity with the enzymatic mechanism of ADA-1, but it has been mainly localized in the extracellular space. Scarce information is currently available about the recently discovered ADA-3 or ADA-like protein (ADAL) [46].

ADA deficiency disrupts the metabolism of deoxynucleotides and S-adenosyl-L-methionine (AdoHcy) — dependent reactions of cellular transmethylation, which leads to the accumulation of toxic deoxyadenosine, which can kill cells, especially thymocytes [47]. In patients with partial or complete ADA deficiency, disorders of purine metabolism can be found, such as an increase in adenosine and deoxyadenosine in blood plasma, deoxyadenosine in urine, and a decrease in ADA activity in erythrocytes [47; 48]. In patients with milder disorders, T-cell lymphopenia often precedes overt immunodeficiency [48].

Purinergic receptors

Most cells express two main groups of purinergic receptors — P1 for adenosine and P2 for ATP, ADP, UTP, and UDP. In turn, receptors of the P2 family are defined as ionotropic (P2X) and metabotropic (P2I). The latter, like the P1 receptors, belong to class A (rhodopsin-like family) of the superfamily of G-protein coupled receptors (GPCRs) [49].

P1 (ADORAs) adenosine receptors. There are four different types of these receptors in this family include A1, A2A, A2B, and A3 receptors, which result in different biological functions [50]. In general, the A1 receptor (A1R) and A3R decrease the cAMP levels, but A2AR and A2BR increase it [24].

A1R mediates the inhibition of adenylate cyclase, induces activation of phospholipase C, and inhibits G-protein-coupled activation of voltage-dependent Ca^{2+} chan-

nels [51]. A1 receptors are found extremely in the CNS, adipose tissue, heart muscle, inflammatory cells especially in neutrophils, and immature DC. These receptors can be activated at 0.3–3 nM concentration of adenosine [52].

It has been shown that their agonist ligands A1R have the therapeutic potential as atrioventricular node block and supraventricular tachyarrhythmia and are candidates for the treatment of bradyarrhythmia associated with interior myocardial infarction, cardiac arrest, cardiac transplant rejection [53].

A2 receptors are classified into the A2A (high affinity, activated by adenosine concentration 1–20 nM) and A2B (low affinity, activated by adenosine concentration more than 1 μM) receptors [54].

A2A receptors are found in the neurons, blood platelets, olfactory bulb, spleen, thymus, leukocytes, heart, lung, and blood vessels [55]. A2A agonist receptor ligands are being studied to cure respiratory disorders, sepsis, reperfusion injury, thrombosis, hypertension, and inflammatory disorders by enforcing and blocking A2AR dependent immunomodulatory mechanisms [56]. Adenosine, by binding to A2A, exhibits anti-inflammatory properties and can suppress inflammation, protect against inflammation in trauma and neurodegeneration [57]. There is evidence that the expression of the A2A receptor on human monocytes is raised by pro-inflammatory cytokines like interleukin-1 (IL-1) and tumor necrosis factor (TNF) [58]. Ligation of A2A receptors on monocytes and macrophages increases the secretion of IL-10, which has immunosuppressive properties [59].

A2B receptors are expressed in the gastrointestinal tract, cecum, colon, bladder, lung, blood vessels, adipose tissue, adrenal gland, brain, kidney, mast cells, stem cells, lymphocytes, and macrophages [60]. IFN-γ prevents activation of the adenosine receptor (A2BR) on macrophages, thus maintaining their activation during inflammation. A2B receptors in mast cells cause an increase in the production of pro-inflammatory mediators in inflammatory airways disease. A2B agonist receptor ligands have therapeutic potential in allergic reactions, asthma, and pulmonary inflammation [61].

A3 receptors inhibit adenylate cyclase activity, while stimulate directly phospholipases C and D [57]. They are highly expressed in testis (rat), mast cells (rat), cerebellum, hippocampus, thyroid, most of the brain, adrenal gland, spleen, liver, kidney, heart, DC, lymphocytes, eosinophils, and macrophages, but not present on human lung mast cells [62]. A3 agonist receptor ligands are studied in experimental trials of cardiac ischemia, arrhythmias, glaucoma, asthma [63; 64].

P2 receptors. Unlike the P1 receptor, P2 receptors recognize nucleotides. They have an affinity range for extracellular nucleotides from 100 nM to 1 mM. The P2 receptors are classified into two main families, P2Y and P2X. P2Y (G protein-coupled) receptors trigger downstream effector signaling pathways ending with increased concentration of intracellular Ca^{2+} or cAMP. P2X, the ATP-gated ion channels, allow Na^{+}, Ca^{2+} influx, and K^{+} efflux [65]. P2Y receptors have eight subtypes include P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, P2Y13, and P2Y14. P2X receptors have seven subtypes with six homomeric contain P2X1 to P2X5 and P2X7 and six heteromeric P2X1/2, P2X1/4, P2X1/5, P2X2/3, P2X2/6, and P2X4/6 receptors [66; 67].

The P2X7 receptor is a rather unusual receptor/channel since it generates a non-selective plasma membrane pore that allows the transit of aqueous molecules with a molecular weight up to 900 Da [68]. P2X7 receptor plays a key role in immunity and inflammation as a major activator of the NLRP3 inflammasome, and therefore a powerful trigger of IL-1β

and IL-18 maturation and secretion [11]. Also, P2X7 stimulates reactive oxygen species (ROS) production in macrophages via the mitogen-activated protein kinase (MAPK) and the nicotinamide adenine dinucleotide phosphate oxidase complex. This receptor is involved in several inflammatory conditions, such as sepsis, arthritis, granuloma formation, and others [68].

P2Y1, P2Y2, P2Y4, and P2Y6 receptors can activate Gq and phospholipase C-β (PLC-β), producing inositol triphosphate (IP3), which raise intracellular Ca^{2+} level through its release from intracellular stores, and diacylglycerol (DAG), which in turn activates protein kinase C (PKC) [16].

P2Y12, P2Y13, and P2Y14 receptors activate protein Gi and can inhibit adenylyl cyclase, and therefore the reduction of cAMP levels. Stimulation of P2YR11 via activation of Gq and Gs triggers the growth of intracellular Ca^{2+} and cAMP [69].

Conclusion

The first evidence of purinergic cell-to-cell signaling was presented by Bernstock in the 1970s, and by 2009 all components of the purinergic signaling pathway had already been identified. Since 2015, the complex of proteins and cofactors that are involved in the fundamental aspects of purinergic signaling and cellular homeostasis is termed "purinom" [70]. There is no longer any doubt that purinergic signaling leads to a wide range of cellular responses. Purinergic regulation has been studied as an important factor of hormone secretion, neurotransmission, and neuromodulation, in the regulation of specialized functions of various organs, such as kidneys, liver, cardiovascular, immune, and respiratory systems [11]. In the study of cognitive functions, special attention was paid to the study of purinergic receptors on neurons and immune cells of the brain. However, the range of cells for which the purinergic regulation is extremely important continues to expand. Recent studies in mice revealed that signaling through the erythrocyte adenosine A2B receptor (ADORA2B) promotes O_2 release to counteract hypoxia, and the loss of erythrocyte–specific A2B receptors enhances brain hypoxia and accelerates the early onset of age-related impairments in spatial learning, memory, and hearing ability [71].

It should be noted that purinergic mediators/autacoids are involved in different ways in many tissues. For instance, if the level of adenosine in the blood raises, blood circulation in the coronary arteries may improve. However, in the lungs, adenosine causes a narrowing of the airways, and in the kidneys, it reduces the production of renin (angiotensinogenase), which reduces renal blood flow. In addition, adenosine is an inhibitory neurotransmitter in the brain. During nighttime sleep, the level of adenosine in the brain increases, improving sleep quality and suppressing arousal [72]. This versatility of activity creates conditions for many "side effects" and determines the difficulties in the clinical use of purine mediators. Currently, for the prevention of thrombotic complications in diseases of the cardiovascular system, clopidogrel, an antagonist of the P2Y12 receptor, is widely used. The efficacy and safety of this drug, which inhibits platelet activation, is because P2Y12 receptors are present only on platelets and microglia. Therefore, the structure of the drug, which does not allow penetration through the blood-brain barrier, ensures its accurate targeting on platelets. However, for other purines, it should be noted that purinergic mediators/autacoids are involved in different ways in many tissues. For instance, if the level of adenosine in the blood raises, blood circulation in the coronary

arteries may improve [72]. For other purine receptors, such selective localization is not typical, which complicates the use of their agonists/antagonists in clinical practice.

So far, purinergic regulators are being actively studied as resources for the diagnosis or treatment of various diseases (Table) [54].

Table. **Examples of purinergic receptor subtypes as therapeutic targets. Some of them are already in clinical use, while others are in clinical trials or proof of concept studies (adapted from [54])**

Receptor type	Family	Subfamily/Class		Diseases
Adenosine Receptors	P1	A1		Supraventricular tachycardia
		A2A		Scleroderma
				Parkinson's disease
				Coronary artery disease
				Neurodegenerative and psychiatric diseases
		A2B		Asthma
		A3		Psoriasis
	P2	P2X	P2X3	Chronic cough
				Hypertension
				Visceral pain
				Overactive bladder
				Migraine
				Atherosclerosis
			P2X4	Neuropathic pain
			P2X5	Inflammatory bone loss
			P2X7	Atherosclerosis
				Infection
				Abdominal pain
				Rheumatoid arthritis
				Neurodegenerative and psychiatric diseases
				Asthma
				Autoimmune diseases
				Ulcerative colitis/Crohn's disease
				Renal disease
				Cancer
		P2Y	P2Y2	Dry eye
				Cancer
				Muscular dystrophy
			P2Y12	Thrombosis and stroke
				Osteoporosis

Finally, it is important to note that purinergic signaling is a very early evolutionary mechanism, that was formed in bacteria [73]. It has been shown that bacteria have their enzymes of purine metabolism and in some cases use them to stimulate excessive inflammation. With uncontrolled inflammation, the conditions for stimulating a protective immune response are disrupted and bacteria escape from destruction in phagocytic cells, which makes it possible to establish chronic forms of infection [74]. Thus, the study of the characteristics of purinergic regulation in infections can indicate new ways to increase resistance to infectious and non-infection diseases.

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Received: July 17, 2021
Accepted: October 17.2021

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PUBLIC HEALTH AND HEALTH CARE

UDC 616.98:578.834.1-082.4

Operating experience of a multidisciplinary medical hospital under the conditions of reprofiling to receive patients with the new coronavirus infection COVID-19

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For citation: Nikitin A. E., Shikhova Yu. A., Velichko I. V. Operating experience of a multidisciplinary medical hospital under the conditions of reprofiling to receive patients with the new coronavirus infection COVID-19. *Vestnik of Saint Petersburg University. Medicine*, 2021, vol. 16, issue 3, pp. 203–210. https://doi.org/10.21638/spbu11.2021.307

The purpose of our work was to increase the efficiency of medical care provided to patients with the new coronavirus infection COVID-19 who were admitted to a multidisciplinary hospital, based on a retrospective analysis of the work carried out to reorganise material-technical and personnel support, organise operations in an unfavourable epidemiological situation in the period from 16.05–06.11.2020. During the specified work period, data on 677 hospitalised patients were analysed. The practical experience of the FGBUZ CCH RAS demonstrated the feasibility of a quick response to unfavourable development of the epidemiological situation associated with the spread of COVID-19 via solving the problem of reorganising a multidisciplinary hospital, taking into account the implementation of organisational measures that provide the material and technical basis for the diagnosis and treatment of patients and measures aimed at preventing the spread of infection among medical personnel and patients. Our data confirmed that complications related to infection with COVID-19 and which led to the need to use intensive care measures were more typical for people in the older age group: with an average age of 57 ± 6 years for men and 64 ± 7 years for women that were admitted to the hospital. A set of measures to ensure the safety of personnel involved in providing medical care to patients with the new coronavirus infection minimises the risks of personnel infection.

Keywords: new coronavirus infection COVID-19, conversion of a multidisciplinary hospital, unfavorable epidemiological situation, personnel safety, prevention of risks of infection.

Introduction

The significance of the provision of timely medical care to the population, as well as the protection of medical personnel in the context of the COVID-19 pandemic in Russia, is associated with alarming statistics on the number of cases in the country: as of 13/11/2020, the number of cases is 1858568, recovered — 1388168, deaths — 32037 (1.7 % of the number of cases)[1].

The pandemic of the new coronavirus infection has affected not only the healthcare system but all spheres of society's life — economic, social, political and spiritual.

The search for ways to overcome the pandemic has contributed to the intensification of scientific research in almost all subject areas. As a result of a search for scientific publications on the topic of a pandemic of the new coronavirus infection only on the largest Russian information and analytical portal in the field of science, technology, medicine and education — Scientific Electronic Library (http://www.elibrary.ru) by the search query "COVID-19" (as of 13.11.2020), 5798 scientific articles were found that were published in 2020, of which 52 articles were in the thematic section "Medicine and Healthcare" and considered the issues of reorganising domestic healthcare system in the context of a pandemic caused by the single-stranded shell SARS-CoV-2 virus[2].

At the same time, primarily the recommendations of the World Health Organization and, first of all, the experience of the People's Republic of China [1–3] are considered; world data on the aetiology, pathogenesis, clinical features of coronavirus infection COVID-19 are summarised [4–8]; the course of the epidemic process in conjunction with the ongoing anti-epidemic measures in the Russian Federation is studied [9].

Additionally, despite the extensive anti-epidemic measures, the successful development of vaccines, the issue of the COVID-19 pandemic remains tense, which, in turn, emphasises the need to adjust the strategy and tactics of treating the new coronavirus infection, to improve the existing methodological approaches to its prevention, diagnosis and treatment recommended by the Ministry of Healthcare of the Russian Federation[3].

In the spring of 2020 period of the pandemic, new data on safety and risk of pharmacotherapy used in treatment [10], the role of age, concomitant diseases and the activity of the renin-angiotensin-aldosterone system in the manifestations of COVID-19 have already been obtained and published [11].

The generalisation of data on the provision of medical care to and treatment of patients with COVID-19 provided in the article by Zhirnov (2020) based on 55 foreign sources allows to apply a differentiated approach to treatment regimens at the early (etiotropic) and late (pathogenetic) stages of the disease already today using, at an early stage, chemotherapeutic agents aimed at various viral targets: inhibitors of viral RNA polymerase, inhibitors of the viral protease Mpro, inhibitors of proteolytic activation of viral

[1] About confirmed cases of the new coronavirus infection COVID-2019 in Russia [electronic resource]. Website of the Federal Service for Surveillance on Consumer Rights Protection and Human Welfare. Available at: https://www.rospotrebnadzor.ru/ (accessed: 13.11.2020). (In Russian)

[2] Website of the scientific electronic library [electronic resource]. Available at: http://www.elibrary.ru (accessed: 13.11.2020).

[3] Temporary guidelines "Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)" of the Ministry of Healthcare of the Russian Federation. Version 7 dated 06.03.2020. [Electronic resource]. Available at: http://edu.rosminzdrav.ru/fileadmin/user_upload/specialists/COVID-19/MR_COVID-19_v7.pdf (accessed: 13.11.2020). (In Russian)

protein S, which facilitates the virus entry into the target cell, inhibitors of viral deproteinisation in cell endosomes, preparations of exogenous interferon, natural preparations and recombinant virus neutralising antibodies; and, at the second stage, when the multiplication of the virus declines and the threatening pathological processes of excessive inflammation, acute respiratory distress syndrome, pulmonary tissue edema, hypoxia dominate, the use of pathogenetic agents, such as extracorporeal blood oxygenation, detoxification, anti-inflammatory and antibacterial therapeutic measures and activities are most important [12].

For stable and effective work of medical organisations during a pandemic, another important consideration is to ensure the safety of and prevent the spread of infection among medical workers and ensure their social protection [13].

In this regard, consideration and exchange of experience in medical organisations' work in the conditions of admitting patients with COVID-19 for treatment is a necessary component of improving the provision of high-quality and timely care to patients, which determined the relevance of our work [4].

The aim of the study was to increase the efficiency of the provision of medical care to patients with COVID-19 admitted to a multidisciplinary hospital based on a retrospective analysis of the work carried out on during the reorganisation and the process of ensuring the hospital's functioning in an unfavourable epidemic situation.

To achieve this goal, the following main tasks were solved step-by-step: 1) reorganising of a multidisciplinary hospital during an unfavourable epidemiological situation to admit patients with COVID-19 while ensuring the safety of medical personnel; 2) improving the diagnosis of the disease and its complications, as well as the tactics of treating patients with COVID-19 with varying severity of the disease; 3) analysing statistical data on patients and hospital work for the period of admission of patients with COVID-19; 4) summarising the hospital's experience in providing medical care to patients with COVID-19.

Methodology

The study used data on the medical activities of the Federal State Budgetary Institution of Healthcare Central Clinical Hospital of the Russian Academy of Sciences (FGBUZ CCH RAS) in the period from 16.04.2020. to 06.11.2020, which, in accordance with the Order of the Government of the Russian Federation dated 02.04.2020 No. 844-r from 13.04.2020, was re-profiled to provide medical care to patients with the new coronavirus infection COVID-19, and, in accordance with the Letter of the Founder of the FGBUZ CCH RAS — the Ministry of Science and Higher Education dated 05.06.2020 No. MN-9/994-AM "On the coordination of the phased restoration of the organisation's core activities," stopped hospitalisation of patients with the new coronavirus infection COVID-19 or with suspicion of it.

To reorganise the hospital to ensure the provision of medical care to patients with the new coronavirus infection COVID-19, the experience of infectious diseases hospitals and previously reorganised hospitals, as well as the recommendations of the Ministry of Healthcare of the Russian Federation that were existing at that time, were used.

During the period of admission of patients with the new coronavirus infection COVID-19, the following data on 677 hospitalised patients were analysed: age and sex composition of patients, including those in the intensive care unit, the average length of stay in

the hospital, the degree of lung damage (based on CT) and the proportion of the use of artificial lung ventilation, the number and structure of lethal outcomes of the disease.

The proportion of medical workers who became ill (infected) with the new coronavirus infection caused by the COVID-19 virus was determined.

Results

FGBUZ CCH RAS is a multidisciplinary medical institution, which includes inpatient departments of therapeutic and surgical profiles, as well as a widely presented diagnostic base. Despite the vast availability of all the necessary equipment for work in "peacetime", the transition to the operating mode of an infectious diseases hospital required significant changes in the structure of the institution, in its mode of operation, logistics and routing of the flow of patients and staff, as well as the implementation of measures to ensure the safety of life and health of medical personnel.

To solve the first task — the reorganisation of a multidisciplinary hospital during an unfavourable epidemiological situation while ensuring the safety of medical personnel — first of all, to prevent the infection from leaving the zone where patients were located, it was necessary to organise a sanitary checkpoint with a system of locks, a separate exit, changing rooms for personnel, sanitary rooms and showers, areas for putting on personal protective equipment. In the shortest possible time, design and implementation documentation was prepared, a sanitary checkpoint with the necessary set of premises was organised in the hospital's basement.

For the work of the administrative staff, auxiliary services, temporary modular structures were erected in the immediate vicinity of the medical building.

For effective functioning in the mode of an infectious diseases hospital, the hospital departments were reorganised, six infectious diseases departments were formed to classify the patients by the severity of the disease. To ensure patients' safety, to reduce the spread of infection, a decision has been implemented on their single placement based on the principle of boxed wards.

Medical personnel have been trained on the portal of continuing medical education of the Ministry of Healthcare of the Russian Federation and received certificates in various aspects of providing medical care for the new coronavirus infection COVID-19. In addition, classes were held on compliance with sanitary and epidemiological measures when working with infectious patients. Most of the employees (65 %) acquired experience in providing medical care to patients with coronavirus pneumonia at the Scientific Research Institute of first-aid named after Sklifosovsky in Moscow.

An important component in protecting personnel from infection was the full provision of employees with protective equipment and underwear, footwear, additional fixation of clothing items, and care and hygiene products. The need was calculated based on the necessity to change personal protective equipment (PPE) once every 6–8 hours.

Throughout the entire work period in the conditions of the COVID hospital, experienced medical workers dressed the personnel entering the "redzone". Detailed visual information with the stages of putting on and taking off PPE was posted on the premises. Afterwards, for the rational use of personnel and to reduce the risk of infection, the removal of PPE was carried out under remote video control.

The hospital premises were disinfected with the recommended disinfectants regularly, following the established requirements and with the required frequency.

Delivery of medicines, medical equipment, parcels and transfers was carried out through a system of gateways.

To minimise the risk of contamination, radios were used to communicate with personnel working in the "redzone". Medical records in the "redzone" were kept in electronic form, with the provision of contactless access in the "green zone" over a computer network. An expert group was organised in the "green zone" to work with medical documentation (registration of case histories, processing of statistical information, and current quality examination).

At the entrance and exit from the "redzone", the employees underwent contactless thermometry. A mobile laboratory unit was deployed in which hospital staff gave weekly swabs from the oropharynx and nasopharynx for subsequent detection of SARS-CoV-2 RNA by PCR and ELISA for detecting antibodies to SARS-CoV-2. Thus, all employees were aware of their state of health, and the risk of spreading infection within the team was minimised.

In addition to complying with safety measures in accordance with sanitary and epidemic requirements, during the reorganisation process, it became necessary to reduce contacts of employees with people from risk groups, including family members; staff needed psycho-emotional recovery and good rest after heavy work shifts. In this regard, it was decided to place the personnel in a nearby hotel complex with 2 hot meals a day and organise a transfer to work and back.

When solving the second task — improving diagnostics and treatment tactics for patients with COVID-19 — we relied on the available temporary Methodological recommendations for the prevention, diagnosis and treatment of new coronavirus infection COVID-19 of the Ministry of Healthcare of the Russian Federation4, algorithms and treatment regimens were updated as concurrently with the recommendations. Medical care was provided to patients depending on the severity of the condition, taking into account complications and concomitant diseases.

One of the most important tasks in providing medical care to patients and ensuring their safety was to correctly organise the allocation of incoming patients at the stage of the admission department and their further routing. Thanks to pre-prepared checklists for patient interviews, informed consent templates, standardised referral forms for tests, the average time a patient spent in the admission department was 10–15 minutes. After that, the patient was sent to the CT department. The duration of the patient's stay in the department of radiation diagnostics did not exceed 5–7 minutes.

Our practice of providing medical care has confirmed that computer tomography (CT) plays the most significant role in diagnosing coronavirus pneumonia. The main radiological signs that characterise COVID-19 are the presence of a zone of reduced airiness of the pulmonary parenchyma of the "ground glass" type with or without consolidation areas. The nature of the spread of the inflammatory process depends on the stage of development of the disease and its severity, but most often, it is polysegmental. Additionally, in patients with coronavirus infection, adenopathy of the intrathoracic lymph nodes caused by reactive changes can be determined.

In a reorganised institution, CT was performed for all patients upon admission, the degree of lung damage, the degree of involvement of the lung parenchyma in the inflam-

[4] Temporary guidelines "Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)" of the Ministry of Healthcare of the Russian Federation. Version 7 dated 06.03.2020.

matory process was determined, followed by a decision on the further routing of the patient depending on the severity of the condition and the clinical profile.

As a result of introduced marking of patients using bracelets of different colours depending on the severity of the condition based on the results of CT diagnostics was based on the ward layout, reflecting the presence of an oxygen point, proximity to a medical post (for moderate and severe patients requiring constant visual control), the patient was assigned to the appropriate ward in the shortest time.

The organisation of a linear infectious diseases department for critically ill patients on the same floor as the intensive care unit also reduced the time spent transporting patients.

To monitor the effectiveness of patients' treatment, dynamic CT control was carried out at the frequency recommended by the treatment standards for new coronavirus infection.

During the work of the Central Clinical Hospital of the Russian Academy of Sciences as an infectious hospital, several emergency operations were performed, such as the surgical resolution of acute intestinal obstruction and myocardial revascularization in acute myocardial infarction.

Additionally, during the period of work with the new coronavirus infection, the pathological service did not stop its functioning. The handling of biomaterials obtained from infected patients, the autopsy of the deceased required special conditions for the protection of specialists, regulations for transporting, storing and subsequent burial of bodies, all of which were provided for in the process of reorganisation.

The solution to the third task of the research — analysis of statistical data on patients and the work of the hospital of the FGBUZ CCH RAS for the period of admission of patients with COVID-19 showed that out of 677 patients admitted to the hospital, by gender and age, 321 patients (47.3 % of all hospitalised) were men (average age — 57 ± 6 years), 356 patients (52.7 % of all hospitalised) were women (average age — 64 ± 7 years). Patients spent 8822 days in the hospital; the average time spent in the hospital was 13 bed-days.

There were 115 patients in the intensive care unit, which is 17 % of all hospitalised patients. At the same time, 73 patients in the intensive care unit (63.5 % of those admitted to intensive care) were men with the average age of 66 years ± 4 years; 42 patients (36.5 %) were women, the average age was 70 ± 5 years.

The average age of patients in intensive care was 68 ± 5 years. The average length of patients stay in the intensive care unit was 11 bed-days. At the same time, 64 % of patients from the total number of those admitted to intensive care had lung damages of more than 75 % (CT-3; CT-4), 66 patients (57 % of those who were in intensive care; 9.7 % of all admitted) were transferred on the artificial lung ventilator. 6 people were extubated (9 % of those assigned to artificial lung ventilation). 9 patients were transferred to other medical organisations (8 % of those in intensive care).

Upon the completion of receiving medical care in the hospital, out of 677 patients were discharged home for follow-up care on an outpatient basis — 516 people (76.2 %); transferred to other medical organisations — 97 patients (14.3 %), 4 patients refused treatment (0.6 %). The number of deaths is 60 (8.9 %). Of the 60 deaths, 58 patients (97 % of all deaths; 8.6 % of those admitted) were with the confirmed new coronavirus infection caused by the COVID-19 virus, of which 36 patients (60 % of all deaths; 5.3 % of admissions) had U07.1 Coronavirus infection caused by COVID-19 virus (virus identi-

fied) as the main diagnosis. The average age of patients with fatal outcome was 76 years ± 3 years.

During the entire work period, 474 medical workers were involved in providing medical care, of which 175 are doctors, 201 are nurses, and 98 are junior medical personnel. Of those infected with a new coronavirus infection caused by the COVID-19 virus — 38 employees (8 % of the total number of medical workers), including doctors — 4, nurses — 23, junior medical personnel — 11, no severe cases of the disease among employees were registered.

The solution to the fourth task — a generalisation of the hospital's experience in providing medical care to patients with COVID-19 took place continuously in the process of daily work. The team of the Central Clinical Hospital of the Russian Academy of Sciences searched for new methods of diagnosis and treatment. In particular, a study was conducted on the feasibility of using radionuclide diagnostic methods to assess the effectiveness of treatment of patients with the new coronavirus infection. The result of the work was a conclusion on the feasibility of using molecular imaging methods such as positron emission tomography and single-photon emission tomography for the diagnosis of inflammatory cardiovascular complications in patients with confirmed COVID-19.

Discussion

The practical experience of the FGBUZ CCH RAS showed the feasibility of a quick response to the unfavourable development of the epidemiological situation associated with the spread of COVID-19 by solving the problem of reorganising a multidisciplinary hospital, taking into account the implementation of organisational measures that provide the material and technical basis for the diagnosis and treatment of patients and measures aimed at preventing the spread of infection among medical personnel and patients [14; 15].

Our data confirmed that complications associated with infection with COVID-19 that led to the need for intensive care unit measures are more typical for people in the older age group: with an average age of men of 57 ± 6 years and women of 64 ± 7 years old admitted to the hospital; the average age patients admitted to the intensive care unit was 66 ± 4 years in men; in women 70 ± 5 years. At the same time, 64 % of the total number of patients admitted to the intensive care unit had lung damage of more than 75 % (according to the results of CT-3; CT-4), 66 patients (57 % of the number of persons who were in intensive care, or 9.7 % of all admitted) were transferred to artificial lung ventilation. Data coincide with data of other authors [16].

Conclusions

A set of measures to ensure the safety of personnel involved in providing medical care to patients with the new coronavirus infection minimises the risks of personnel infection.

Our practical experience in reorganising a multidisciplinary institution can be used in the future when working both with patients infected with COVID-19 and in conditions of a worsening epidemic situation with infections with similar spread routes and mechanisms of influence on the body and tactics of treating infected patients.

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Received: July 23, 2021
Accepted: September 2, 2021

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HYGIENE

UDC 613.1:504.062:311

Overview. Analysis of ensuring climate information collection for carrying out social and hygienic monitoring

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For citation: Noskov S. N., Mironenko O. V., Yeremin G. B., Fedorova E. A. Overview. Analysis of ensuring climate information collection for carrying out social and hygienic monitoring. *Vestnik of Saint Petersburg University. Medicine*, 2021, vol. 16, issue 3, pp. 211–223. https://doi.org/10.21638/spbu11.2021.308

Earth's climate change and its adverse consequences are a global problem at the international level. On the territory of the Russian Federation, climatic conditions change approximately 2.5 times more intensively than on average on the planet, average annual temperatures are rising in all physical and geographical regions and federal districts. To solve this problem, the Russian Federation has ratified a number of international documents and developed measures to adapt to climate change. To improve social and hygienic monitoring, — dynamics of changes in air temperature, air velocity, relative air humidity, and atmospheric pressure are used as major indicators in climate assessment, bioclimatic indices being their integral assessment indicators. We can state with good reason that the forecast and meteorological factor effects on human body are the most important links in social and hygienic monitoring. Currently, in spite of many years of research, mechanisms, character and significance of this phenomenon remain largely uncertain. Absence of reliably identified consistent patterns restrains from further research to reveal subtle physiological mechanisms causing human body response to climatic changes.

Keywords: human environment factors, public health, meteorological factors, meteosensitivity, social and hygienic monitoring.

Introduction

Climate (from Greek *klima* — tilt) (inclination of Earth surface to the Sun's rays) is a long-term weather regime corresponding to a particular area. It is caused by a combination of atmospheric, space and terrestrial natural factors which form the weather. Division of the globe into climatic zones: hot, warm, temperate, and cold is related to geographical latitude, from 0 до 30°, from 30 to 45, from 45 to 60 and over 60° latitude.

Depending on average annual temperature and geographical location of the area, 7 major climatic zones are distinguished on the globe, 4 of them being basic climatic zones: equatorial, tropical, temperate and polar, and three being transitional: subequatorial, subtropical and subpolar. Temperate, arctic, subarctic and subtropical zones which in their turn are subdivided, as well, prevail in Russia [1].

Earth climate change and its outcomes is a global problem of the international level. According to the Hadley Center for the United Kingdom's Meteorological service, the global warming rate between 1976 and 2020 is 0.18° per decade, and only during this period the global temperature rose by 0.8 °C. According to Rosgidromet (Federal Hydrometeorology and Environmental Monitoring Service), the average warming rate in Russia is significantly higher than the global one and is 0.51 °C per decade for the same period of 1976–2020[1].

Materials and methods

Cause-effect relationships between population health and impact of human environmental factors, as well as risk and damage from the climate change resulting in increased morbidity and mortality levels among increased risk population groups were studied in this research.

Standard and legal documents, which regulate carrying out social and hygienic monitoring, procedures to assess the degree of natural climate factor effects on population health were analyzed, measures to improve survey, assessment and prognosis of pathological condition development among population caused by unfavourable environmental factors were developed.

Results and discussion

According to the latest edition of the law "On Sanitary Epidemiological Wellbeing of Population" no. 52-ФЗ of March 30, 1999, and to the RF Government Decree no. 60 of February 02, 2006 "On Approval of Regulations on Carrying out of Social and Hygienic Monitoring", monitoring human environment factors, including natural climatic factors, being one of its components, is one of the tasks of social and hygienic monitoring (SHM), performed by Federal Service for Supervision of Consumer Rights Protection and Human Well-being.

Based on monitoring data, Federal Service for Supervision of Consumer Rights Protection and Human Well-being creates a Federal information Stock for SHM data. It is a database on population health status and human environment, developed on the basis of

[1] Report on the peculiarities of the climate in the territory of the Russian Federation for 2020. — Moscow, 2021, p. 104.

regular systemic observations, and a set of regulatory legal acts and procedural documents on the issues of analysis, prognosis and identifying of cause-effect relationships between population health status and human environment factor effects on a human[2].

Currently the Federal Service for Supervision of Consumer Rights Protection and Human Well-being does not carry out monitoring of natural climatic factors in Russia in the framework of SHM.

Control of natural and climatic factors is carried out by local bodies of Rosgidromet (Federal Hydrometeorology and Environmental Monitoring Service). The following indicators are included into SHM: meteorological conditions, degree of temperature inversion manifestations, solar activity, geomagnetic field, ionosphere state, and presence of geopathogenic zones (phenomena)[3].

In accordance with RF Government Decree no. 372 of July 23, 2004 "On the Federal Service for Hydrometeorology and Environmental Monitoring" Rosgidromet is a Federal executive body performing the functions of providing state services in the field of hydrometeorology and related areas, environment and environmental pollution monitoring, state supervision over the activities impact on meteorological and other geophysical processes. There is a unified state database on the state environment and its pollution[4].

According to Procedural guidelines MP 2.1.10.0057-12 "Assessment of risk and damage from climatic changes causing morbidity and mortality level increase in high-risk population groups", meteorological indicators used to assess climate change effect on population health include average daily and maximum indicators of atmospheric air temperature, relative humidity, atmospheric pressure, wind velocity and precipitation amount.

The most prevalent diseases characterized by climatic change sensitivity include:

— respiratory diseases: acute respiratory infections (J00–J22), allergic rhinitis (J30), chronic obstructive pulmonary diseases (J40–J44), bronchial asthma (J45);
— circulatory system diseases: diseases characterized by increased blood pressure (I10–I15), ischemic heart disease (I20–I25), cardiac conduction impairment and arrhythmia (I44–I49), cerebrovascular diseases (I60–I69);
— endocrine system diseases: diabetes mellitus (E10–E14);
— injuries, poisonings and other consequences of external causes: injuries (S00–T14), frostbites (T33–T35), drowning (W69–W70), suicides (X60–X84);
— mental disorders and alcoholic psychoses (F10);
— intestinal infections: salmonellosis (A02), shigellosis (A03) and other intestinal bacterial infections (A04) and poisonings (A05), viral intestinal infections (A08);
— vector-borne diseases: Lyme disease (A69.2), tick-borne viral encephalitis (A84), Dengue fever (A90–A91), West Nile fever (A92.3), yellow fever (A95), malaria (B50–B54), leishmaniasis (B55), African trypanosomiasis (B56), Shagas disease (B57), ochocerciasis (B73), filariasis (B74).

[2] Federal Law No. 52 "On the Sanitary and Epidemiological Welfare of the Population" dated March 30, 1999.

[3] Methodical recommendations no. 2001/83 "Methodology for conducting social and hygienic monitoring", 2001.

[4] Decree of the Government of the Russian Federation of July 23, 2004, no. 372 "On the Federal Service for Hydrometeorology and Environmental Monitoring".

Increased risk population groups for which climatic change health effects are assessed, include:

— children (from 0 to 17);
— elderly persons (60 years and older) and old-aged (75 years and older);
— persons with chronic diseases, suffering from respiratory, circulation nervous, urinary and endocrine system diseases;
— employable age persons, including outdoor workers;
— indigenous peoples.

Assessment of meteorological factor effects on health should be done according to the following indicators:

— population mortality;
— population morbidity by number of persons seeking medical care;
— morbidity by hospital admission data;
— number of population seeking emergency medical aid [2].

Ability of living organisms to respond to weather conditions changes is called meteodependence. The following quantitative clinical tests are used to assess meteotropic responses [3]:

— Kerde index (I_K) is used to characterize autonomic nervous system responses. Positive values of I_K are considered to reflect prevalence of tone of sympathetic division of autonomous nervous system, and negative values are specific for vagotonia, i. e. unstable state of blood vessels;
— Rudder's meteosensitivity test index (G M). Value of G M > 1 corresponds to the presence of meteotropic manifestations;
— Index of seasonal morbidity and mortality Gc = (dI/mI 365)/N, where dI — number of deaths in the i-month of the year being considered; mI — number of days in a month; N — population size.

According to manifestation degree, four types of meteosensitivity can be classified [4]:

Mo — there is no evident sensitivity to weather regime changes.

M1 — meteosensitivity is slightly manifested. In unfavourable weather mild responses appear, mainly general complaints (low mood, headache, inertia, weakness, muscle pain, slight sleep disturbances).

M2 — meteosensitivity is moderately manifested. In unfavourable weather objective disturbances occur (increased blood pressure, sore throat and other symptoms of cold. In cardiovascular disease patients negative ECG deviations, evident decrease of working capacity, occurrence of heart pains).

M3 — high meteosensitivity. Meteopathic responses are manifested in severe degree (hypertensive crisis, respiratory impairment, asthma attacks, angina attacks, angina attacks, aggravation of chronic pneumonia). People belonging to this group of meteosensitivity have got very low adaptation capacity, so they need permanent medical control.

According to the literature data [5] the strongest meteotrophic responses can be seen in blood circulation disease patients: myocardial infarction, hypertension, rheumatism. In some cases percentage of coincidences of aggravations with unfavourable weather types

reaches 72 %. On cyclone and thunderstorm days the number of sudden clinical death cases in ischemic disease patients as well as percentage of acute left ventricular insufficiency increases significantly.

Correlation analysis of the role of meteorological factors in cardiovascular disease pathogenesis showed that January weather severity index (r = 0.57), weather sultriness (r = 0.5), number of humid weather days (r = 0.51), gloomy weather frequency (r = 0.66), number of no-wind days (r = –0.55) are the most significant climatic indicators.

Average daily number of deaths is approximately the same, both on high and low atmospheric pressure days, significant correlations being seen between acute myocardial infarction and the number of days with air temperature difference > 60 °C (r = 0.54) and pressure > 10 hPa (r = 0.52). Increased rate of hypertension disease attacks, is mainly associated with "spastic" and "hypoxic" weather types; in years with frequent recurrence of days characterized by sharp and significant fluctuations of air temperature and atmospheric pressure (over 50 °C and 5–10 hPa) and with greater frequency of "sultry" weather, characterized by low air oxygen concentration, disease incidence rate increases significantly.

Hypertension crises frequency increase associated with weather changes were reported by other authors as well, for example, N. S. Temnikova et al surveyed patients through the entire period of hospital stay (30–60 days), retrospectively studied medical histories of 1801 patients and 24 422 ambulance calls. 54.7 % of hypertension patients and 24.3 % of myocardial infarction patients were meteosensitive, most unfavourable months being March, April, May, December, February.

In 48.2 % of cases meteopathic reactions were observed with a decrease in atmospheric pressure by 5–8 hPa and an increase in relative humidity by 25–30 % in frontal cyclonic weather. Arkhipova I. V. revealed a close correlation mainly between hypertension disease and the number of days with significant diurnal fluctuations in atmospheric pressure (≥ 8–10 hPa) (r = 0.84), frequency of sultry weather days with air temperature ≥ 200 C and air humidity ≥ 80 % (r = 0.5).

It is reported that among rheumatism patients meteosensitivity achieves about 90 %. Meteosensitivity of this disease is classical. Significant temperature and atmospheric pressure fluctuations result in unfavourable effect on the course of rheumatism. In the temperate zone an increase in frequency of aggravations is mainly reported in autumn, winter and early spring — during cold and damp seasons.

Research carried out in Yalta Scientific Research Institute of physical treatment methods and climatology named after I. M. Sechenov showed that over 50 % of chronic nonspecific pulmonary disease (COPD) patients are meteosensitive, and among chronic obstructive bronchitis patients this percentage is 72 %. Weather conditions characterized by rapid approach of weather front, atmospheric pressure drop, high humidity, strong wind, cold snap are most unfavourable for meteosensitive COPD patients.

Analyzed the relationship of COPD and bronchial asthma course with weather conditions showed that in warm season meteopathologic response was seen on the average in 20.2 % of patients (in 28 % of bronchial asthma patients), and in cold season the response was observed on the average in 48 % of the patients (and in 78 % of bronchial asthma patients).

The COPD course is greatly affected by the entire complex of meteorological factors. Bronchial asthma prevalence has got an evident climatic dependence. Bronchial asthma

incidence is mainly reported in areas where the climate is characterized by a combination of high humidity with high or low air temperatures and with a contrasting weather change.

In addition to direct unfavourable effect the weather can produce an indirect one as well. For example, the higher the air humidity, the greater are the effects of chemical and biological allergens. The self-cleaning ability of atmosphere is of certain significance. Low diffusing capacity of atmosphere reduces the comfort of climatic conditions for respiratory disease patients

When analyzing infectious diseases of upper respiratory tract, many researchers emphasize the significance of unfavourable weather conditions in increasing disease incidence.

Correlation analysis of the role of meteorological factors in the incidence growth of acute infectious diseases of upper respiratory tract showed that the Bodman weather severity index (r = 0.8) and duration of low temperature air period (r = 0.5) are the most important climatic indices. Seasonal dynamics of respiratory disease incidence is quite evidently manifested in temperate climate zone and is characterized by increased frequency of attacks in spring (March — April) and in autumn (October — November).

Correlating of acute condition incidence of gastric ulcer and other diseases with weather conditions reveals a significant role of the latter and allows over 30 % of acute condition cases to be attributed to weather-related ones indicates to the significance of meteorological factors for chronic gastrointestinal disease children.

According to his findings, from 41 to 63 % of children suffering from these diseases are weather-sensitive. The number of acute conditions of gastric ulcer increases with unfavourable weather and with pronounced meteorological instability accompanied by significant air temperature fluctuations (r = 0.55) and high weather severity index (r = 0.5).

About 20.3–22 % of all acute conditions in pyelonephritis and 25.1 % in glomerulonephritis are weather-related. According to Grigor'ev, 53.5 % of glomerulonephritis and 40.6 % of pyelonephritis children are meteosensitive. A correlation between renal and urinary tract diseases and winter weather severity index (r = 0.58) and frequency of humid weather periods (r = 0.5) was identified.

The climate of dry and arid steppes of the Kulunda lowland with long hot and dry summer with very high average air temperatures, low humidity, intense solar radiation induces profuse sweating and can be quite favourable for chronic nephritis.

When analyzing the relationship of frequency of seeking medical aid by mental disorder patients and climatic indicators, significant and reliable correlations were found with weather severity index (r = 0.5), frequency of changeable weather with temperature drops in atmospheric air pressure > 10 hPa (r = 0.57) and long-term discomfort period in transitional seasons of the year (r = 0.6).

When assessing weather and climatic factor effects on pregnancy course and outcome, special importance is attached to storm winds and frontal weather. A direct relationship between the occurrence of pregnancy complications and frequency of weather periods with significant pressure drops (r = 0.54).

In the studies by D. A. Chernykh et al. carried out on Krasnoyarsk Territory it was shown that temperature fluctuations (periods of hot and cold weather waves) and mortality jumps related to them, especially caused by cardiovascular and respiratory diseases [6] are significant.

According to E. G. Golovina, various biometeorological indices are used to assess weather conditions from medico-meteorological point of view, such as effective temperature (ET), equivalent effective temperature (EET), normal equivalent effective temperature (NEET), radiation equivalent effective temperature (REET), biologically active temperature (BAT), temperature and humidity index (THI), wind cooling index (WCI), human heat balance equation, Bodman index of climate severity, and from medical point of view, it is advisable to use the wind-cold index (according to Siple), equivalent calm temperature (ECT) heat load index HLI (K. Ya. Kondrat'ev), index of pathogenicity of meteorological information, weather variability index.

Currently about 30 biometeorological indicators are known and used for calculations — indices which are tentatively divided into 7 major groups. The classification was developed by E. G. Golovina and M. A. Trubina and at Russian State Hydrometeorological University, St. Petersburg, and supplemented with the 7th group by S. S. Andreev [7; 8]:

1. Temperature and humidity indicators:
   ET — effective temperature of still air;
   DI — discomfort index (USA);
   DY — discomfort index (Japan).
2. Temperature-wind indicators (cold stress indices):
   W (K) — wind-cold index (according to Siple);
   WC — updated wind-cold index (Kanada);
   S — severity score according to Bodman;
   T — weather severity coefficient according to Arnoldi;
   H — wind-cooling index according to Hill;
   So — weather severity coefficient according to Osokin;
   ECT — equivalent calm temperature.
3. Temperature-humidity-wind indicators (for shady spaces):
   ET — equivalent-effective temperature (thermal sensitivity index, taking into account wind effect);
   EET — equivalent-effective temperature;
   NEET — normal equivalent-effective temperature (thermal sensitivity index, taking into account wind effect for a dressed person).
4. Temperature-humidity-wind indicators (taking into account solar radiation):
   REET — radiation equivalent effective temperature, assessed by expert as the most informative index;
   BAT — biologically active temperature;
   Tred — reduced temperature indicator according to Adamenko and Khairulin;
   Qs — net heat balance of human body according to Rusanov;
   C — clothes insulation, unit clo;
   Climate discomfort coefficient according to V. I. Rusanov.
5. Pathogenicity and climate variability indicators:
   I — pathogenicity index of meteorological situation (according to Boksha);
   ρO_2 — partial oxygen density according to Ovcharova;
   CWM — class of weather of the moment according to Rusanov;
   K — variability index of CWM according to Rusanov;
   BISM according to Belkin;

MHI — meteorological health index according to Bogatkin;
G — thermoregulation mechanism intensity index according to B. A. Aizenshtadt;
N — heat load index according to K. Ya. Kondrat'ev.

6. Indices of climate continentality:
K_G — according to Gorchinskii;
Kkhr. — according to Khromov.
7. Indices characterizing the state of atmosphere:
Ii — summary index of atmospheric pollution.

In view of keeping favourable living conditions for population and development of required preventive measures, B. B. Prokhorov suggested to determine comfort degree of the area on the basis of analysis of about 30 human environment parameters: duration of periods with different air temperatures, climate continentality, total sum of heating degree/days, soil and water ability to self-purification, biota character, seismicity, permafrost, risk of floods, mudflows, avalanches, prerequisites for diseases and conditions of their manifestations, prevalent pathology among various population groups, presence of factors contributing to or preventing from recovery of patients and etc.

Degree of comfort was suggested to be assessed on a 5-point scale. According to this scale the regions considered are divided into comfortable, precomfortable, hypocomfortable, uncomfortable and extreme ones.

Comfortable areas (the most favourable for human habitation) are the territories where factors which significantly complicate work, life, recreation of people, are absent or are insignificant. Adaptation of newcomer population takes place here quickly and without complications.

Precomfortable areas are territories where negative impact of natural factors on population health is seen for a short time and is slightly manifested. The adjustment of newcomer population is accompanied by a moderate stress of adaptive systems of the body with a tendency to quick compensation.

Hypocomfortable areas are territories within which natural factors complicate normal working conditions, life and recreation conditions of population. Adaptation of newcomer population takes place here with a strong strain of adaptive systems of human body with gradual compensation.

Uncomfortable areas are territories where most of the year natural conditions complicate work, life and recreation of people, and certain natural conditions have a strong negative effect on population health (especially that of old-aged and children).

Adaptation of migrants is accompanied by strong strain of adaptation systems of the body with complicated compensation.

Extreme regions are areas within which natural conditions, practically all year round, sharply complicate work, life, relaxation of people, and parameters of some environmental factors reach values which are critical for health and life. Adaptation of migrants here takes place with very strong stress of adaptation systems, with a tendency to decompensation [8; 9].

E. S. Andreeva et al. suggest calculation of certain biometeorological indicators, as well as determination and interpretation of integral index of climatic comfort (IICC). In particular, at the first stage, a thermal effect on the body is assessed, using such param-

eters, as: equivalent effective temperature (ET), biologically active temperature (BAT), radiation equivalent effective temperature (REET), heat balance of human body (Q).

The second stage of technique implementation involves assessment of degree of pathogenicity of meteorological conditions (I). At the third stage it is supposed to assess potential of atmosphere for its self-purification (Км). Integral indicator of bioclimatic comfort resulting from the described procedure implementation is suggested to be determined as a sum of scores of bioclimatic assessment resulting from 3 stages.

Suggested integral indicator, which is the sum of points of all three stages of climatic comfort assessment, is universal for any studied area and enables to identify such parameters as: comfort, discomfort and moderate discomfort. At the same time, important effect of meteorological factors on health is taken into account, as well as the possibility of reducing atmospheric pollution due to its self-purification potential [10].

V. V. Vinogradova, taking into account varying climatic conditions on the territory of Russia, suggested to use the Universal thermal comfort index (UTCI). UTCI index reflects equivalent ambient temperature which has the same physiological effect on humans as the actual environment. This indicator was initiated by the Commission of the International Society for Biometeorology [12].

According to S. V. Tkachuk, the most promising in terms of predicting the comfort of weather conditions are the indicators which take into account the effect of accumulation of negative impact of certain conditions. The American HIS index (Heat Stress Index) is one of such indices developed to determine heat load in summer season. The distinctive feature of this index is a consideration of a number of variables, which as well as the major meteorological parameters affect heat perception: wind velocity, cloudiness and solar radiation. Moreover, none of the indices developed earlier takes into account accumulation of negative effect of heat over a certain period, for example, several days [13].

To systematize research and apply it to the needs of economic activity in climatology, the concept of climatic scales is used. The main ones are macro, meso and micro scales. The macroscale is used in meteorology and climatology to study processes and phenomena comparable in size to hemisphere or its large regions (seas, continents). Mesoscale climate changes are usually understood as processes occurring under the effect of a large city or some area of a large lake, river, valley, mountain range, etc.

Each building site and individual objects have their own microscale climate, i. e. — microclimate on their territory and in the immediate vicinity of it. The most significant sanitary and hygienic indicators of the microclimate which affect thermal state, include: air temperature and its relative humidity, air velocity, thermal radiation of human body and surrounding objects, which determine the possibility of heat exchange between the body and the environment, and achievement of thermal balance of the body.

A thermal state in which there is slight stress in thermoregulation is defined as a state of thermal comfort. Therefore, climatic parameters of thermal comfort are used as a hygienic standard for microclimatic conditions. In general, "microclimatic standard" should provide an optimal state of the body which is characterized by an insignificant strain of functional systems. At the same time, hygienic regulation cannot be limited to establishing only optimal parameters for certain factors.

Simultaneously "allowable" limits of their fluctuations must be determined. These limits are set depending on the nature of outdoor activity and physical activity level typical for this activity. According to the degree of influence on a person's wellbeing and on

his working capacity, microclimatic conditions can be divided into: optimal, allowable, harmful and dangerous (extreme).

Optimum microclimate conditions are characterized by such parameters of microclimate indicators which under their combined effect on a human can provide keeping up of a thermal state of the body. In these conditions a minimum in thermoregulation mechanism strain is seen, whole-body and/or local discomfort heat sensations are absent, which is a prerequisite for maintaining high working capacity.

In an optimal microclimate a comfortable thermal state of human body is provided. Allowable microclimatic conditions are characterized by such parameters of microclimate indicators that under their combined effect on a human can cause such change of a thermal state in which a moderate strain of thermoregulation mechanisms is observed. In this case a slight general and/or local discomfort in heat perception can occur.

Meanwhile, relative thermal stability is preserved, temporary decrease of working capacity can take place, but the health is not impaired. Such microclimate parameters are admissible at which the thermal state of the body can be considered satisfactory.

Harmful microclimatic conditions are microclimate parameters, which under their combined effect on a human can cause changes in the thermal state of the body: pronounced general and/or local discomfortable sensations of heat, a significant stress in thermoregulation mechanisms, a decrease in working capacity. At the same time, thermal stability of a human body and health preservation are not guaranteed. The degree of harmfulness of microclimate is determined both, by values of its components, and their exposure duration.

Extreme (dangerous) microclimatic conditions are microclimate parameters, human exposure to which even for a short time (less than 1 hour) cause a thermal state change characterized by excessive stress of thermoregulatory mechanisms which can result in health disturbances and death risks. Moreover, extreme indicators can include heatstroke, cold stress and squall wind effects [14].

A retrospective analysis showed that the forecasting institutions of Hydrometeorological Service started providing doctors and public with medical weather forecasts since 1963. Clinical testing of the method for assessing meteosensitivity using medical types of weather was the development of interregional schemes of medical weather characteristics for certain regions of the country. These included central regions of the European territory of Russia, the Black Earth Zone, Leningrad region, the Volga region, the Far East, Crimea, Kyrgyzstan, Uzbekistan, Latvia, Lithuania, etc.

Identifying and prevention of adaptive-meteotropic syndrome contributed to a decrease in the frequency of complications and relapses of the underlying disease, and increased treatment effectiveness.

Timely consideration of medical weather forecasts enabled medical personnel to perform the prevention of meteotropic reactions in in-patient, home, and out-patient settings.

Thus, the use of a complex of collective and individual measures on days with weather of type III and IV reduced the frequency of pathological meteotropic responses in various diseases by 80–90 %, contributed to the patient adaptation (if he was sent to a sanatorium) to climatic conditions change and to sharp weather fluctuations.

Diagnostics of increased meteosensitivity state was carried out according to the anamnesis, clinical and meteorological monitoring and the use of diagnostic test indices.

The average observation period enabling to obtain objective information on meteosensitivity, is 45–60 days, and should not be less than 3–4 weeks. It is required that 3–4 days with sharp changes in weather were reported during the observation period.

An important principle of clinical and meteorological monitoring is the application of the method of superposition of short-period epochs — an analogue of the method of superposition of epochs of A. L. Chizhevsky for heliosociological studies. The method of superimposing short-period epochs assumes simultaneous observation of a group of sick and healthy persons for 30–45–60 days, which enables to identify their meteosensitivity, its severity degree and to determine the type of meteotropic reactions [16].

In current conditions characterized by global climate change and growing anthropogenic pollution of environment, prevention and correction of meteopathic responses in healthy and sick people, are becoming increasingly important. To solve this problem new approaches to monitoring meteo-helio-geophysical factors are used, taking into account their information value and evidenced relatedness to changes in the functional state of the human body.

New diagnostic and treatment procedures for early detection and correction of meteopathic reactions, especially those relating to cardio cardiorespiratory system, are being developed. Within the framework of these studies, Yu. A. Rakhmanin et al. [17] developed new scientific, organizational and procedural approaches to development and implementation of programs to prevent the adverse effects of global climate change on RF population health.

The work performed evidenced the prospect of creating a mathematical model for the development of increased meteosensitivity in response to the influence of unfavourable meteorological factors, followed by the formation of recommendations for its use in personalized programs of sanatorium-resort treatment of meteo-dependent patients.

E. G. Kameneva [18] identified the most informative physiological indicators and suggested a meteosensitivity assessment method in coronary heart disease patients and changes in systolic blood pressure in healthy subjects, clinical application of which contributed to the increase of effectiveness of vascular event prevention and development of arterial hypertension in coronary artery disease patients.

Often an increase in overall mortality among acute myocardial infarction patients is reported a few days before meteorological factors start changing; a method of early weather forecasting and informing health authorities for them to take required organizational long-term measures [19].

Results of analysis of regional features of meteorological conditions of urbanized Caucasian midlands made it possible to improve the System of Sanitary Hygienic Monitoring and develop measures to improve survey, assessment and prognosis of development of acute pathological condition of cardiovascular system in population, caused by unfavourable environmental environmental factors [20].

Stupishina O. M. et al. suggested and tested a model for early assessment of natural and climatic factor effect on population health [21].

Special emphasis should be given to the contribution of photochemical formation of formaldehyde, which may significantly exceed direct emissions from natural, industrial, mobile and agricultural sources. In winter or on summer nights in cities direct formaldehyde emission may be more important than those from the secondary sources.

Among the sources of urban atmospheric air pollution by formaldehyde, especially in large cities, vehicle exhaust plays an important role. Formaldehyde concentration in

atmospheric air has got a seasonal and diurnal character and depends on meteorological factors. In daytime and in summer with high temperatures and solar activity, formaldehyde concentration increases greatly [22].

In order to improve social and hygienic monitoring, the determining indicators in climate assessing are dynamics of changes in air temperature, air velocity, relative air humidity, atmospheric pressure, — for the assessment of which bioclimatic indices will be integral indicators. It can be quite reasonably stated that the forecast and assessment of meteofactor effects on a human body are the most important links in social and hygienic monitoring.

Currently, in spite of many years of research, — mechanisms, character and significance of this phenomenon remain largely uncertain. The lack of reliably identified patterns restrains further research aimed to reveal subtle physiological mechanisms, which cause human body responses to climatic factor changes. Inconsistencies of findings of numerous studies carried out by domestic and foreign researchers can be explained by natural climatic features of various regions of the world, insufficient number of observations and errors in statistical processing of data obtained.

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Received: July 18, 2021
Accepted: September 30, 2021

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