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MATHEMATICAL MODELS OF RESPIRATORY AND BLOOD CIRCULATORY SYSTEM

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Aim. To analyze modern approaches to mathematical modeling of respiratory and blood circulatory systems of human organism.

Methods. Comprehensive review of scientific literature sources taken from domestic and foreign resources, databases.

Results. Historical information and contemporary data concerning mathematical modeling of functional respiratory and blood circulatory system were summarized and analyzed in present review; current trends in approaches to the construction of these models were revealed.

Conclusions. Two main approaches to the mathematical modeling of respiratory and blood circulatory systems exist for today. One of them is the construction of models of mechanics of respiration and blood circulation. They were based on the models of mechanics of solid deformable body, thermomechanics, hydromechanics, and mechanics of continuum media. This approach supposes the use of complex mathematical apparatus, including Navier-Stokes equation, which makes it possible to obtain a number of theoretical results, but it is hardly usable for real problems solutions at present time. The second approach was based on the model of F. Grodins, who represented the process of the breath as controlled dynamic system, written using ordinary differential equations, in which the control was carried out according to the feedback principle. There was significant number of modifications of this model, which made it possible to simulate various disturbing influences, such as physical activity, hypoxia and hyperemia, and to predict parameters characterizing functional respiratory system under these disturbing influences.

Key words: mathematical model of respiratory system; mathematical model of blood circulatory system; hypoxic state; theoretical analysis.

Human lives in the Nature during all his life and interacts with the environment. During this human receives various disturbing influences, both external (changes in gas composition and pressure of inhaled air, temperature of environment) and internal (changes in metabolism, viral infections). A number of laboratory and instrumental methods are developed to analyze the state of organism, with which one can get information about his current state, but nothing more. The task of adequate modeling of processes in living organism is one of the most relevant for contemporary medicine. The processes that ensure the viability of human organism are so complex and interrelated that the closest possible interaction of mathematicians, biologists and physicians is necessary for their modelling.

The purpose of the work was to analyze modern approaches to mathematical modeling of respiratory and blood circulatory systems of human organism.

Physical formulations of problems that arise during the study of normal and pathological processes in human organism have become significantly more complicated in contemporary reality [1]. Along with the expanding capabilities of computer modeling, the requirements for mathematical models that describe the processes occurring in human organism have increased. The objects of modern mathematical modeling are almost all major human systems and organs — respiration and blood circulation, heat exchange and thermoregulation, central and peripheral nervous systems, digestion, kidneys and liver, immune system and carbohydrate metabolism system, musculoskeletal system, organs of hearing, vision, leather, and etc. Simultaneously, modeling can be carried out at the cellular and gene levels. Mathematical models that allow the simulation of mechanisms of the start and course of diseases, from wounds and oncological diseases curing to issues of immunology, drug delivery, and the creation and functioning of various organs were of considerable interest too. Mathematical models of a number of organs and parts of organism (skin, bones, muscles, etc.) were based on mechanical models known from the mechanics of a solid deformable body. For the problems of hemodynamics, functioning of respiratory system, digestion, and excretory system, hydrodynamic formulations based on the Navier-Stokes equations were used. Significant part of mathematical models of thrombosis, functioning of stomach, skin, and treatment of a number of diseases by thermal or chemical effects was based on the equations of reaction-diffusion and heat conduction. The dynamic systems of ordinary differential equations formed the basis of models of respiratory and blood circulatory system, transmission of nerve impulses, cellular interactions, functioning of gene networks, and etc. Naturally, hybrid models that take into account the fullest possible interaction and interrelationships of the processes under the study were the most in demand.

The most characteristic numerical models for a number of biomedical processes constructed using the classical theory of continuum mechanics had been analyzed in review [1]. Reviews of this class of problems were included into [2–18] too; they were interesting, although partially not very recent ones. Brief, but rather capacious review was presented in [19].

Evolutionary models were of great interest too; they allowed simulating various disturbances in organism and predicting its stationary state at a given level of disturbances. It was possible to manage various influences, consider their combination, study and predict the functional state of human organism under various extreme influences by simulating these influences on mathematical model. Currently, this is especially important when choosing a strategy and tactics for medical cure of organism affected by the SARS CoV-2 virus.

Today, mathematical and simulation models are used widely to study the regulations of physiological processes. Mathematical modeling is an effective tool that allows simulating extreme disturbances on human organism and predicting its reactions to disturbances in the internal and external environment, while modern diagnostic methods characterize only the current state of organism. The advantage of using simulation models is the ability to obtain information at the level inaccessible to modern invasive methods. An overview of mathematical models of various organs and systems of organism one can find in [1, 20]. This direction was based primarily on the works of P.K. Anokhin [21, 22], whose main ideas were the theory of functional systems and application of systematic approach to the study of physiological functions. F. Meyerson built a coherent theory of organism adaptation, in which, among other functional systems, the respiratory and blood circulatory systems were singled out as most noticeably responding to the changes of human life conditions [23, 24]. It was also demonstrated [25–27] that if the human organism was presented as a chain with “weak link” in terms of reliability theory, the respiratory and blood circulatory system can be seen as such “weak link”.

Widespread computerization had formed the bases for the development of theoretical foundations of any phenomenon or process by simulating this phenomenon or process using computer. It is clear that for the development of computer model the development of mathematical model had to be done previously. This is especially true for physiology and medicine. If in physics and chemistry the experimenter deals with inanimate objects with which any experiments can be performed, then here, in addition to ethical standards, there are quite a few limitations associated with inability to experiment with various extreme perturbations and limitations of diagnostic methods. Mathematical modeling allows

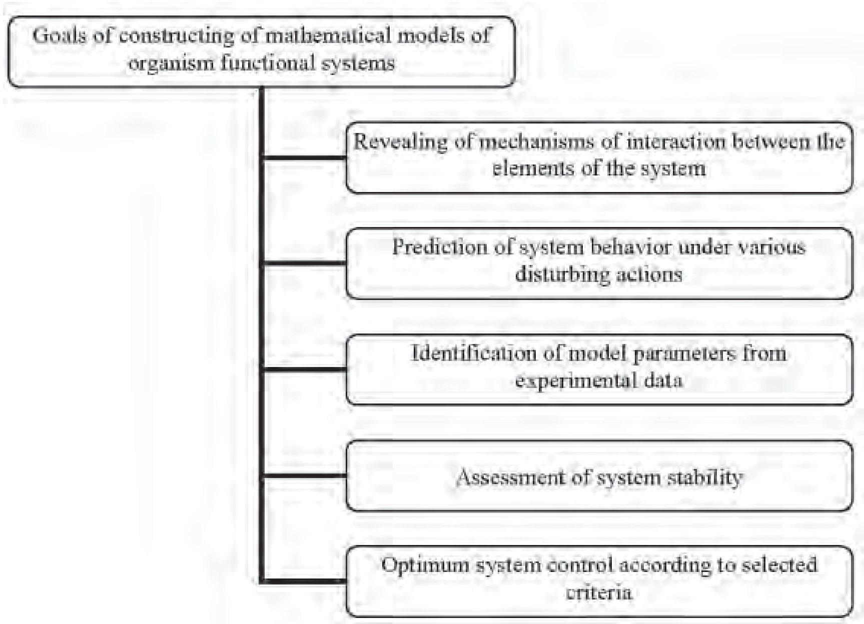

Fig. 1. **Goals of modeling of organism functional systems**

us to control various influences, study and predict the behavior of such complex system as human organism. The complexity of the task of mathematical models constructing of organism functional systems was primarily due to the extreme complexity of considered biological system, functioning of which depends nonlinearly on large number of factors, on almost every element of living organism, and these dependencies largely remain unformalized even at the level of physiological descriptions. Therefore, analytical methods of solution can be applied in rather narrow scope, and the main means for studying of real problems related to the study of respiratory and blood circulatory systems are computational methods for problems solution with computer.

When choosing and formulating a mathematical model, the determining factors are the object, purpose, method and methods of modeling [Anokhin]. For mathematical modeling methods of dynamic systems theory are used. Means — differential and difference equations, methods of qualitative theory of differential equations, computer simulation. The goals of mathematical modeling of organism functional systems were shown on Fig. 1.

The main principle of mathematical modeling of complex systems is the principle of optimality [28]. It is necessary to note that the principle of optimality has been used for a long time in biology.

Methods of theory of optimal control in physiology

The methods of the theory of optimal control of respiration had aroused the constant interest of researchers of physiological systems, primarily due to the ideas about the perfection of regulatory mechanisms in living systems. The specificity of application of methods of the theory of optimal control in the study of physiological systems is that the criteria for their optimality are unknown. The task of the study was to establish whether given physiological system was an optimal control system and what exactly the criterion for its optimality was. Accordingly, such studies include the following steps:

– selection of the control object and the construction of its mathematical model;

– selection based on the data of experimental studies of a hypothetical optimality criterion;

– construction of mathematical model of the optimal control system, including the control subsystem (optimizer) and the control object;

– study of the model of control in order to verify its adequacy.

At each of these stages, significant difficulties arise, both experimental and theoretical. Therefore, the number of works on this issue were insignificant and they had been done only recently [29, 30]. The indicators, linked with energy transformation in organism the most often played the role of criterion of optimality, since the economy of physiological functions in general case is beyond the doubt. The model of regulation of parameters of external respiration and organism blood supply developed by Yu.M. Onopchuk, was based on the assumption concerning the optimality of the system for regulation of organism oxygen regimes [31]. The criterion for optimality of the functional state of oxygen transport system (OTS) can be the sum of energetic costs of organism [32]:

$$W = W_H + W_L + W_E + W_T,$$

where W_H, W_L, W_E, are the values of power consumed by the heart, lungs and hematopoietic system, respectively, W_T – is the power of extraction in the absence of physical activity. The values W_H, W_L, W_E, W_T are the functions of parameters φ_I, characterizing the functional state of the OTS. The optimal values of these parameters can be determined by solving equations $\frac{dW}{d\varphi_i} = 0$.

Based on this approach, it is possible to investigate how close the OTS control algorithms are to optimality and within what limits of changes in the conditions of oxygen transport this closeness is maintained.

An adaptive neural network model had been developed; it detected the optimality and homeostatic characteristics of respiratory control system [33]. The theoretical analysis of the effect of main parameters changes of the inhaled air flow on the distribution of air and mean barometric pressure in the lungs was made [34]. A method has been developed to differentiate the process of lung ventilation into two images: the first characterizes the optimal distribution of inhaled air for each of the ventilated lungs; the second characterizes the optimal perfusion, which corresponds to the lowest possible average alveolar pressure. Using the concept of the work of the heart based on the end-systolic volume-pressure dependence, the conditions for optimal interaction of the left ventricle with the arterial system were determined [35]. A mathematical model of the left ventricle of the heart has been developed, reflecting both hemodynamics and the processes of myocardial enlargement depending on the load and metabolic conditions [36]. The model was used to determine the optimal myocardial function for given arterial load and vice versa. The optimal size of the left ventricle was determined from the conditions of maintaining normal oxygen consumption under the different conditions of chronic load on the heart rate. A mathematical model of the human circulatory system, which includes a description of the systemic and pulmonary circulation and baroreflex regulator for heart rate and peripheral circulation [37], was used for theoretical analysis of the problem of optimal control of blood circulation with complete replacement of the heart or its partial unloading after the connection of auxiliary pump. An optimality criterion for blood circulation control was proposed. This criterion was based on minimizing the deviations of variables of the model state, for them the arterial and venous pressures in the systemic and pulmonary circulation were chosen. In Murray's model of optimal branching of vessels [38], the radii of the vessels were related to the viscosity, the rate of vascular exchange, and the rate of blood circulation in such a way as to minimize the overall (hydraulic and metabolic) work of the system.

In [39], the problem of optimal structural and functional organization of the external respiration and circulatory system was mathematically formulated as optimization problem with chosen objective function and restrictions. As a result of its solution, the optimal values of structural and functional parameters were found, which can be compared with the corresponding experimental values.

We would like to mention the work [40] as well, which analyzes publications related to extremal principles in mathematical biology.

Mathematical models of the respiratory system

According to [41], two approaches can be used for the mathematical analysis of physiological functions: the data models and system models. In the first case, the task is to build mathematical function that describes a set of input data more accurately, for example, a statistical data model. But physiological features of the structural and functional organization of the modeled object are not taken into account at all in it. Models of the second type are based on physiological principles and hypotheses regarding the structural and functional organization of the modeled object. The purpose of modeling is to test the physiological hypothesis, which is the basis of the model, and to study basic physiological mechanisms of the phenomenon or process under investigation. It should be noted that usually the results of analysis of physiological experiment with the construction of data models were used as initial data for the next stage of investigation — systemic analysis of these data models and development of mathematical model of studied system functioning, aimed on studying of fundamental physiological mechanisms underlying its functioning.

Among the models of the respiratory system, a real breakthrough was the model of F. Grodins [42], in which the respiratory system is represented as dynamic system, so, this allows using appropriate mathematical apparatus. There are a large number of mathematical models of respiratory system, which are based on Grodins model, in which rather complex mathematical apparatus is used. Without touching of models of "black box" type, which also have the rights to exist because they allow us to identify cause-and-effect relationships and reliable dependencies at the population level, but do not allow us to analyze the processes occurring within the system, we will pay more attention to structural models. Such models were developed on the basis of the laws and hypotheses on the structuring and functioning of biosystems. Mathematical models of respiratory system differ depending on the purpose of investigations. There are widespread such models of respiratory mechanics, in which the lungs are represented by elastic shells connected to the atmosphere by a tube with some hydraulic resistance [43], which make it possible to obtain the simplest relationships between physical parameters characterizing the functioning of the lungs, but do not take into account spatial diagnostics in human lungs.

One of the most developed approaches was based on quasi-one-dimensional hydraulic models on graphs [1]. Detailed description of such models one can find in [44, 45], where a complex model of the respiratory system and closed model of blood flow was built on the basis of distributed dynamic system on graphs. The elastic properties of the tube walls, which determine the relationship between the pressure in the tube and its cross section, are determined by additional equation of state. Dynamic model of air entering the alveoli from the external environment with each breath (alveolar volume) was presented also in [45].

Brief review of human lung models that vary in complexity, starting from the simplest, which were presented as rigid container contacted with the atmosphere, to a model in which the volume and pressure that change under the influence of muscle work, taking into account gas exchange with blood and perfusion blood had been suggested in [46]. Two-chamber lung model consisting on alveolar space through which the blood was perfused and anatomical dead space was described in [47]. This model is used to estimate the minute volume of blood circulation. One-dimensional model of air transfer from trachea to alveoli was analyzed in [48], taking into account the gas exchange of respiratory gases with blood and blood perfusion. An assumption about the correct dichotomy of airways and laminar flow of the air, and the explanation of the reasons of existence of exactly 23 generations of airways was done, although the Weibel model by itself was proposed much earlier [49]. However, we have to note that the assumption about laminar flow in airways was substantiated by domestic scientists on mathematical model [50] much earlier. Similar results were described too in [51]. With intensive development of computational methods of gas dynamics and means of their implementation three-dimensional models of air flow had been started to develop, the air by itself was considered as multicomponent mixture of gases. A review of these models can be found in [52].

The models that describe the process of gas exchange in the lungs and operate with averaged parameters were much more interesting. In [53], other version of the model was proposed in which the total mass of the lungs and chest were assumed to be distributed over the surface of any reservoir of variable volume. The mechanical properties of such reservoir were determined by integral characteristics that described the resistance of airways, the inertia of the air in them, the elasticity of the lungs and chest. The model was based on the ideal gas equation under isothermal conditions, the equation of the motion of reservoir shell and the integral equation of air movement in respiratory tract. This model was developed further in [52], where the equation of the model [53] was written not for the entire volume of the lung, but only for its individual elements, into which air enters through one of respiratory tubes.

It was written in [1] that in recent years, the flow of air in the upper respiratory tract and in whole respiratory tract had been studied intensively using realistic 2D and 3D [54–56]. The study of air movement in nasal cavity, in particular, has many analogies with classical problems of aerohydrodynamics and is of great interest to contemporary medicine. This is due to the facts that now new methods of drugs administration through the nose by inhalation into the lungs or directly on the mucous membrane of the nasal cavity are being actively developed. In [56] such studies were carried out on the basis of Navier-Stokes equations with reproduction of real geometry of respiratory tract, obtained on the basis of analysis of the results of computer tomography.

Mathematical model of human respiratory system was proposed in [52], which contained a set of three connected sub-models that describe the breathing process as a set of synchronized gas dynamics processes in large airways, air movement in a deformable saturated porous medium, and gas exchange (diffusion) through biological membrane. This model was positioned by the authors as sub-model of multilevel model of the entire human organism.

Linear graphs were uses for the development of dynamic model in dissertation [57]. Line graphs of respiratory system have been developed to include all energy domains with sensors linking them together to represent complex dynamic system. Mathematical model of lung mechanics had been developed, including the properties of alveolar tissue and surfactant, which created acceptable values of pulmonary pressure and volume in comparison with the data of healthy patients, patients with acute respiratory distress syndrome (ARDS). The model described time-varying alveolar compliance, which provided better understanding of lung diseases. Using analysis of sensitivity, it was shown that the concentration of surfactant and the parameter of collagen stiffness influenced strongly on the variables of lung mechanics. In addition, the model was proved to be stable and reliable under various perturbations. The model was a set of ordinary differential equations that could be implemented to allow testing of scenario "what if" by changing certain parameters. Using patient data and method of parameters estimation, a personalized version of the model can be obtained. One step more was done to personalized medicine in this dissertation with other physiology-based model and optimization algorithms that improve patient health estimation, diagnosis, and therapy. The dynamic system of the lungs was described, including:

- a module of lung mechanics that described quantitatively the changes in lung pressure and volume;
- alveolar elasticity module which determined alveolar compliance as a function of surfactant concentration and lung fiber elasticity;
- module of the respiratory and thoracic mechanics, which calculated chest movement and pleural pressure changes in process of respiratory muscles contraction and relaxation during breathing (diaphragm and intercostal muscles);
- system of microcirculatory exchange, described the transport of fluid (water) and mass (protein) between alveoli and pulmonary capillaries;
- lung gas exchange system, which quantitatively described the transport of carbon dioxide and oxygen from the lungs into the blood of pulmonary capillaries;
- pulmonary circulation module;

Each module was developed basing on the latest knowledge of lung physiology and validated using patient data when they were available, or published and validated physiology-based models when these data were not available. This dynamic respiratory system could be used to describe the state of healthy people and people with various pathologies. The model made it possible to enter individual patient data and test various therapeutic scenarios in order to select optimal therapy for the patient. In addition, systems identification techniques can be applied to this model or part of it to achieve personalized medicine for better diagnosis and treatment of diseases. For the estimation of the state of lungs health of particular patient, a simplified model of lung mechanics had been developed. Using this simplified model, the parameters which reflected the state of lung health and functionality, i.e. the mechanical properties of the lungs (resistance and compliance) and the efforts of patient's breathing, it was possible to evaluate pulmonary syndromes or diseases such as ARDS and COPD (chronic obstructive pulmonary disease); these diseases caused changes in lung resistance and compliance. Tracking of these two parameters can lead to better diagnostic of disease and easier monitoring of respiratory disease progression. Non-linear, model-based, constrained optimization algorithm has also been developed to estimate lung resistance, lung compliance, and patient inspiratory effort caused by inspiratory muscle activity.

The author also suggested to use linearized version of this model and system identification methods to evaluate not only changes in compliance, but also the properties of the fiber or surfactant that caused these changes. Thus, the model can also mimic the condition of some COVID 19 patients with ARDS. According to [58], 20–30% of patients with COVID 19 admitted to the Department of intensive therapy had severe hypoxemia associated with low values of corresponding parameters.

In some literature sources [59] one can find also such approaches to study of respiratory system as [60–78]: modeling of lung mechanics was given in [69, 70], and modeling of gas exchange — in [71, 72, 75]. Articles [70, 73, 74] provided examples of the development of controllers for the regulation of respiratory system and virtual laboratories designed to simulate the respiratory and cardiovascular systems [65, 66]. The article [59] suggested a simple model that provided a linearized description of pulmonary ventilation and gave some equations that described the basics of chemical regulation of pulmonary ventilation. The processes associated with lung ventilation were discussed, and this formed a basis for overview of other respiratory functions and physiology of some respiratory diseases [65]. The main role was to provide oxygen, which is essential for tissue metabolism, and to remove metabolic by-products such as carbon dioxide. In the nature, complete gas exchange is achieved by passive diffusion through the air-blood barrier between capillaries and alveoli. This requires, in the case of changing load conditions, the maintenance of an appropriate pressure gradient across the barrier, which is achieved by changing the rate of entry of fresh air into the alveoli. As a result of this exchange, the blood flowing from the lungs through the pulmonary veins contains a high O_2 concentration and a low CO_2 concentration. The reverse process of metabolism is carried out in the tissues, where O_2 is consumed and CO_2 is produced as well as metabolic by-products. Four main parts of the respiratory process were being considered:

- Pulmonary ventilation, which includes the flow of air between the atmosphere and alveoli of the lungs in both directions.
- O_2 and CO_2 diffusion between alveoli and perturbed elements of the blood
- O_2 transport and CO_2 ejection in blood and body fluids to the cells and from them.
- Regulation of ventilation and other aspects of breathing.

Only processes related to lung ventilation were discussed in [59]. One of the models describing the human cardiovascular system was represented by the system of 13 differential equations [61–63]. The model consists on two series-connected circuits (systemic blood and lung) and two pumps (left and right ventricle).

Mathematical models of circulatory system

As for mathematical models of blood circulatory system, there are many investigations in framework of this topic exist too. First of all, this is due to the fact that the study of physiological and pathophysiological processes in cardiovascular system is a relevant topic of many contemporary studies [79].

The main functional role of cardiovascular system is blood transportation. The heart provides blood flow in the system of blood vessels. The blood vessels through which the blood flows from the heart to periphery form arterial system. The vessels that collect blood and carry it to the heart form the venous system. A detailed description of the circulatory system and the formulation of the corresponding tasks was given in [4, 5]. In these monographs mechanical behavior of blood, mechanical behavior of the heart, static and dynamic properties of the heart, microcirculation, transcapillary transport of substances, mechanical properties of blood vessels and blood movement in them, as well as mechanics of pulmonary circulation were described.

The blood circulatory system is one of the most popular objects in medicine for all who study blood hydrodynamics [1]. Possible physical problem statements were associated with the description of general blood circulation in human organism [80–86], blood circulation in individual vessels [83, 87] and organs — in heart, kidneys, brain [80–82, 88, 89] for healthy organism or damaged one. To study the general patterns of blood flow in organism and individual organs, the most popular models on graphs are currently used. Classical hydrodynamic formulations based on the Navier-Stokes equations were primarily associated with 2D and 3D modeling of blood flow in large and small vessels, taking into account the elasticity and multilayeredness of vessel walls, multicomponent blood and complex rheology.

In review [1], the models of cardiovascular system were divided into such classes (Fig. 2).

Over the past thirty years, several key approaches have been formed. They made us possible to describe local and systemic processes associated with blood flow, which have different degrees of spatial representation, which depends on the applied problem being solved. Usually, for this was used mathematical apparatus, that included algebraic and differential equations [90]. Averaged models of this type are not demanding on computational resources and contain small number of parameters that are easily determined for particular organism; but, unfortunately, it reflects general physiological patterns only [79]. More complex models require the use of more complex mathematical apparatus. Thus, a detailed description of the blood flow in large vessels was carried out using the Navier-Stokes equation in two or three measurable approximations [91].

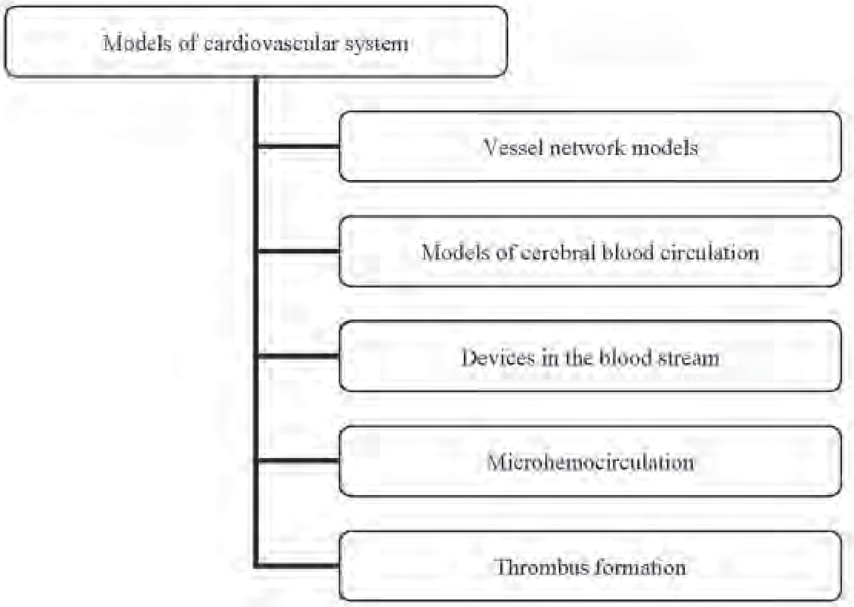

Fig. 2. **Models of the cardiovascular system analyzed in [1]**

The methods for solving of nonlinear partial differential equations in three-dimensional domains of complex shape were used in this approach [92, 93]. In this case, the problem of constructing of three-dimensional geometry corresponding to the shape of vessel or vascular bed aroused. The use of two-dimensional or three-dimensional models also required the setting of boundary conditions at the boundaries through which blood flows, the tasks of rheological properties of blood, taking into account the mobility of the vascular wall, the elastic properties of the wall, the pressure of surrounding tissues, etc. All this makes the use of such models quite inefficient; in addition, it requires the use of significant amount of computing resources. Although the area for the application of following models is typical: three-dimensional analysis of blood circulation parameters in aorta [94], in the main cerebral vessels [95], in aneurysm [96].

Current information on the functional interaction of respiratory and blood circulatory systems under various conditions of organism's vital activity was presented in [97]. Particular attention was paid to adaptive changes in respiratory and hemodynamic parameters in extreme conditions. Basing on the data from literature sources and our own research, physiological parallels were done between intersystem relationships of biomechanics of respiration and hemodynamics under conditions of normal gravity and weightlessness.

It was stated that all systems of organism are involved in maintaining of homeostasis at adequate level for metabolism, but external respiration and blood circulation play decisive role. These systems demonstrate certain independence, characteristic patterns of functional organization and they are in close connection with other parts of the gas transmission system. The often manifested synchronism in changes in respiratory movements and blood pressure under various influences indicates the anatomical and functional relationship between respiratory and vasomotor centers.

In [98] was represented mathematical model of hemodynamics under mechanical influence on the vessels, proved the existence of a smooth solution on the edge, presented numerical implementation of the model, discretized the compatibility conditions, verified the convergence of the numerical solution in uniform norm. There were also tested and numerically simulated following problems: test, autoregulation in separate vessel, occlusion test, blood flow in the coronary arteries, blood flow was also modeled in the lower extremities when running and walking, blood flow was simulated in stenosis of the femoral artery, blood flow in the coronary artery was simulated with increased external counterpulsation, the calculation of the fractional blood flow reserve with using a model of coronary circulation, calculations of coronary hemodynamics in multivessel lesions of the coronary arteries before and after stenting. In the model there were united such components as: models of the muscle pump, autoregulation, enhanced external counterpulsation, as well as coronary circulation, taking into account the functioning of myocardium. The model is based on the previously developed one-dimensional model of hemodynamics and supplemented with models of mechanisms of autoregulation, elasticity of the vascular wall, coronary circulation, with increased external counterpulsation and muscle pump. The disadvantages of proposed model include the discreteness of the recalculation of parameters of vascular elasticity, while in real organism autoregulation occurs continuously. Input data were obtained from clinical examination, in particular angiography, computed tomography and magnetic resonance imaging, as well as the data of medical diagnoses. The lack of information about the structure of the networks was proposed to be solved by replacing the entire large circle with one integral vessel, which will have the same effect on the arteries of the heart as the entire network of vessels had.

The dissertation work [99] attracts the great interest because it represents developed global model of cardiovascular and respiratory systems. The cardiovascular part of this model was based on the four-component Grodins model and included modifications by Kappel and Peer. Respiratory part was based on two-chamber model developed in [100]. The basic models had been revised, expanded and generalized. As subsystems, the model included: systemic and pulmonary circulation, left and right ventricles, tissue and pulmonary compartments. Mechanisms such as Frank-Starling law, the Bowditch effect, and variable cerebral blood flow were included. In particular, the model was adapted to the situation of dynamic exercises. The initial anaerobic energy supply, the mechanism of metabolic autoregulation in peripheral regions, dilatation of pulmonary vessels were taken into account. In the model, the control parameters were the heart rate and alveolar ventilation. Simulation of rest and physical activity was possible. The disadvantage of this model was that it takes into account the control of the functional respiratory system only by linear feedback, in which the quadratic cost functional is minimized, while there are other control loops existed — by perturbation, by anticipation, etc. [101],

Integral mathematical model of the human cardiopulmonary system was presented in [102, 103], in which were described the problems of interaction between cardiovascular and respiratory systems. It should be noted that this approach was applied by a few authors only, and these works were a pleasant exception. Integrated cardiorespiratory model has been developed for mathematical description of interaction between the cardiovascular and respiratory systems, as well as their main short-term control mechanisms. The model was compared with the data from open-data sources of human and animal investigations. Article [102] was devoted to the development of models for normophysiology. It includes cardiovascular circulation, respiratory mechanics, tissue and alveolar gas exchange, and short-term neural control mechanisms acting on both cardiovascular and respiratory functions. The model has hundreds of parameters and variables representing physical and physiological properties of human cardiopulmonary system. It can simulate many dynamic states and scenarios. The model was able to simulate physiological variables commonly registered for adults under normal and pathological conditions and to explain the main mechanisms and dynamics.

Further development of this approach was [103], which emphasizes the importance of testing the model for abnormal or pathological conditions in order to prove its consistency and validates the model under conditions of hypercapnia and hypoxia. The authors of this article had focused themselves on testing of cardiopulmonary model under the conditions of hypercapnia and hypoxia by comparing the results of the model with population-averaged cardiorespiratory data presented in literature. The utility of this comprehensive model was demonstrated by testing of internal consistency of modeled responses for significant number of cardiovascular variables (heart rate, blood pressure, and cardiac output), respiratory variables (respiratory volume, respiratory rate, minute volume, alveolar ventilation), and partial pressures and stresses CO_2 over a wide range of perturbations and conditions; namely, hypercapnia at 3-7% CO_2 levels and hypoxia at 7–9% O_2 levels with controlled CO_2 (isocapnic hypoxia) and without control (hypocapnic hypoxia). Finally, the analysis of sensitivity was done to identify the role of main mechanisms of cardiorespiratory control triggered by hypercapnia and hypoxia.

Another extension of the Grodins model was the development described in [104], which is a computational model of human respiratory control system, which is the extension of the model in [105]. The model combined an accurate description of installation with new design of the control part, which considers minute ventilation as the sum of central and peripheral components. To ensure that the developed model was stable and enough reliable to serve as a test platform for ventilation control hypotheses, the authors modeled a number of complex physiological conditions, in particular, the response to eucapnic hypoxia, development of periodic breathing during hypocapnic hypoxia, and the open-loop response to hypercapnic step. These stationary and transient responses of the model were compared with the results of similar physiological experiments. It was assumed that for a certain value of arterial pO_2, the steady-state difference between cerebral and arterial pCO_2 remained approximately constant depending on arterial pCO_2. The model shows that hypoxia-induced changes in cerebral blood flow contribute significantly to the reduction in ventilation observed during eucapnic hypoxia. The model demonstrates periodic breathing caused by hypoxia, which can be eliminated by small increase of carbon dioxide in breathing mixture. The dynamics of hypercapnic ventilation response of the open model approximated well the experimental data.

To predict changes in ventilation, blood gases, and other critical variables under conditions of hypocapnia, and these conditions in combination with hypoxia, a model [106] was developed, which was based also on the model [105]. Refinements of the model concerned the description of:

- influence of blood gases on cardiac output and cerebral blood flow;
- acid-base balance in blood and tissues;
- binding of O_2 and CO_2 with hemoglobin;
- respiratory-chemostatic controller.

The controller consisted on the central and peripheral parts. The ventilation response was induced by the central chemoreceptor, and it is a linear brain function of pCO_2 above the threshold. The peripheral response had both a linear term, similar to that for the central chemoreceptors, but depending on carotid body pCO_2 and with other threshold, and a complex, non-linear term, including the multiplication of individual terms, including the carotid body pO_2 and pCO_2. Being together, these terms form "bent-leg" ventilation curves plotted in dependence on pCO_2, which form a fan-shaped family for various values of pCO_2. With this chemical regulator, the model accurately describes a wide range of experimental data under conditions of exclusively pCO_2 changes and under conditions of short-term hypoxia combined with pCO_2 changes. This model can be used for precise descriptions of changes in ventilation and breathing gases during the ascent and brief-term stay at altitude.

Complex mathematical model [107] was proposed to simulate the exchange, transport, and accumulation of oxygen and carbon dioxide in adults; and model ability to provide realistic responses under various physiological conditions was evaluated. The model is three-compartmental (i.e. lungs, body tissues and brain tissues) and includes control part that regulates alveolar ventilation and cardiac output; the model integrated dynamically the stimuli from peripheral and central chemoreceptors. New realistic dissociation curve for CO_2 was included; it based on two-buffer model of acid-base chemical regulation. In addition, the model takes into account relevant physiological factors such as buffering, non-linear interaction between chemoreceptor reactions for O_2 and CO_2, lung shunt, dead space, variable time delays, and the Bohr and Haldane effects. When simulating hypoxia and hypercapnia modes using this model, obtained results were consistent with those obtained experimentally in the state of n as with dynamic, rest, load and recovery in terms of such parameters as kA ventilation and partial pressures of gases, concentrations of pCO_2, HCO_3, and hydrogen ions in the blood.

The model [108] allows simulating the response of respiratory and blood circulatory system to aerobic exercise for healthy individuals and individuals with heart failure. Physiological response to exercise is seen now as an important tool that can help in diagnosis and treatment of cardiovascular disease. That is why several mechanisms are needed to ensure higher cardiac output and higher oxygen delivery to the tissues. The paper presented fully closed cardiorespiratory simulator that reproduced the main physiological mechanisms occurred during aerobic exercise. The simulator provided also insight into the impairment of these mechanisms in heart failure and their impact on portability limitation of physical exercises. The simulator consists on a model of cardiovascular system, including the left and right part of the heart, the circles — pulmonary and systemic blood circulation. This latter was divided into exercising and non-exercising compartments and it is controlled by baroreflex and metabolic mechanisms. In addition, the simulator includes breathing model that reproduces gas exchange in the lungs and tissues, ventilation control and the effect of its mechanics on cardiovascular system. The simulator had been tested and compared with literature data at three different workloads while cycling (25W, 49W and 73W). The results demonstrated that the simulator was able to reproduce the reaction to the load in terms of: heart rate (from 67 to 134 bpm), cardiac output (from 5.3 to 10.2 l/min), blood flow in the legs (from 0.7 to 3 .0 l/min), peripheral resistance (0.9 to 0.5 mmHg/(cm3/s)), central arteriovenous oxygen difference (4.5 to 10.8 ml/dL), and ventilation (6,1–25.5 l/min). The simulator was adapted further to reproduce the main disturbances observed in heart failure, such as reduced sensitivity of baroreflex and metabolic control, decreased perfusion in the training area (from 0.6 to 1.4 l/min) and hyperventilation (from 9.2 to 40.2 l/min). Thus, the simulator is a useful tool for describing the basic physiological mechanisms that operate during the training. The model can reproduce how these mechanisms interact and how their damages can limit physical performance in case of heart failure. Thus, the simulator can be used in future as testbed for various therapeutic strategies aimed at improving of physical performance in patients with cardiopathy.

In [109], an original mathematical model was proposed for studying the response of cardiovascular system to dynamic load, including pulsating heart, pulmonary and systemic blood circulation, separate description of vascular bed in active tissues, local metabolic vasodilation in these tissues, and the mechanical effect of muscle contractions on venous return. In addition, the model provides a description of respiratory response to exercise and various neural regulatory mechanisms that affect cardiovascular parameters. All parameters in the model were given in accordance with physiological data from scientific literature sources. The model was used to simulate a stationary value of main cardiorespiratory values at various levels of aerobic exercise and time pattern in transition phase from the rest to moderate exercises. The results showed that, with appropriate parameter settings, the model was able to mimic accurately the cardiorespiratory response over the entire range of aerobic exercises. The model may be useful for improving of understanding of exercise physiology and as educational tool for analyzing the complexity of cardiovascular and respiratory regulation.

Integrated mathematical model [110] focused on predicting the response of healthy person at rest and aerobic exercise to study the response of cardiorespiratory system to physical activity. The paper outlines the construction of the model and carried out comparative analysis with known models, like integrated cardiorespiratory model. The model includes cardiovascular circulation, respiratory mechanics and gas exchange system, as well as cardiovascular and respiratory regulators. Each system was based on previously recorded physiological models and includes known mechanisms related to the dynamics of aerobic exercise. The simulation results were compared with experimental data in steady state and transient conditions. Predictions of proposed model replicate closely the experimental data, showing overall the smallest prediction error (10.35%), the fastest settling time for cardiovascular and respiratory variables, and overall the fastest and most similar transient responses. These results indicate that the proposed model was suitable for predicting the cardiorespiratory response of healthy adults under the conditions of rest and aerobic exercise.

An analysis of mathematical modeling of the response of blood pressure and heart rate to submaximal loads was carried out in [111]. Cardiovascular homeostasis was studied at rest and during physical loading.

Mathematical model of CO_2 influence on cardiovascular regulation was proposed in [112]. The effect of CO_2 pressure changes in arterial blood on cardiovascular system was analyzed using mathematical model. This model is an extension of previous one [109], which already included the main reflex and local mechanisms triggered by changes in O_2 and CO_2. New aspects covered by the model included O_2-CO_2 interactions at peripheral chemoreceptors, the effect of local changes of CO_2 on peripheral resistance, direct response of central nervous system (CNS) to CO_2, and control of central chemoreceptors on ventilation and respiratory movements. volume. Statistical comparison of the results of model simulation with various experimental data was carried out. This comparison suggests that the model is able to mimic the acute cardiovascular response to changes in blood gases under various conditions (normoxic hypercapnia, mechanically ventilated hypercapnia, hypocapnic hypoxia, and hypercapnic hypoxia). The model relates registered responses to complex overlay of many simultaneously operating mechanisms (baroreflex, peripheral chemoreflex, CNS response, lung stretch receptors, local effect of gas tension), which can be activated differently depending on the specific studied stimulus. However, while some experiments can be reproduced using one basic set of parameters, reproducing of other experiments requires a different combination of mechanism strength (in particular, different local mechanism of CO_2 strength on peripheral resistances and CNS response to CO_2). Based on these results, some suggestions were presented to explain the striking differences reported in scientific literature. The model can provide reliable support for the interpretation of physiological data on acute cardiovascular regulation and can cause the synthesis of conflicting results into a single theoretical setting.

Integrated model of human ventilation control system was developed to determine the response to hypercapnia [112], which included such chains of mass transfer and mass exchange of respiratory gases as lungs, brain tissues, other tissues, and various types of feedback mechanisms. All these chains included peripheral chemoreceptors in carotid body, central chemoreceptors in medulla oblongata, and central respiratory depression. The latter acted by reducing responses of central nervous system to afferent activity of peripheral chemoreceptors during prolonged hypoxia of brain tissue. In addition, the model takes into account local adjustments in blood flow in response to O_2 and CO_2 changes in pressure in arterial blood. In this study, the model was validated by simulating the response to quadratic changes of alveolar pCO_2 at various constant levels of alveolar pO_2. The results demonstrated good agreement with the data given in scientific literature sources. Subsequently, the analysis of sensitivity of the main feedback mechanisms in the response of ventilation to CO_2 was performed. The results showed as well that the ventilatory response to CO_2 stimulation in hyperoxia can be almost entirely attributed to the central chemoreflex, while in normoxia peripheral chemoreceptors also made some contribution. Contrary to this, the response to hypercapnic stimuli during hypoxia involved complex overlay of various factors with incommensurable dynamics. Thus, the results indicated that the ventilatory response to hypercapnia during hypoxia is more complex than that provided by simple empirical models, and the distinction between central and peripheral components based on time constants can cause mistakes in understaning.

The same authors [113] developed an integrated model of human ventilation control system: to study the response to hypoxia, they simulated long-term isocapnic hypoxia on it at normal alveolar pCO_2 (40 mm Hg = 5.33 kPa) shows the occurrence of a two-phase response, characterized by an initial peak and subsequent hypoxic decrease in ventilation.

Improved dynamic model of respiratory response to physical activity was described in [114]. Modeling of respiratory system had been studied comprehensively in stationary conditions to simulate sleep disorders, predict its behavior in respiratory diseases or irritants, and model of its interaction with mechanical ventilation. The purposes of this study were following. Firstly, to analyze both the dynamic and static responses of two known breathing patterns to stimuli with physical loadings, using a sequence of increasing exercise stimuli (to analyze the response of the model when applying stepwise stimuli) and experimental data (for the estimation of possibility predictions by each model). Secondly, to propose changes in the structures of the models to improve their transient and stationary characteristics. Universalism of the resulting model compared to other two models was shown in accordance with the ability to mimic ventilatory stimuli such as exercises, with proper regulation of arterial blood gases, suitable time constant, and better adaptation to experimental data. The proposed model corrected the breathing pattern in each respiratory cycle using an optimization criterion based on minimizing the work of breathing by regulating the respiratory rate.

The monograph [78] provides a brief overview of human respiratory system and qualitatively describes the processes and components that will be combined for modeling. Ventilation was described by a linear differential equation with lumped parameters, taking into account of resistance R and elasticity E. Further expansion of the model assumed inertia, non-linear elastic behavior, variable resistance and some other characteristics. Future this model was integrated into more complex structures. The lung there was imagined as a set of interconnected pipes through which, according to Poiseuille's law, a viscous liquid flows, while the flow rate is proportional to the decrease of the pressure. The model also takes into account the inertia, which plays significant role in upper respiratory tract. The airways were divided into different zones and Navier-Stokes equation was solved in the upper zone. Further, phenomena of the movement of oxygen from the lungs into the blood were considered; further were taken into account the phenomena of diffusion through different barriers, and saturation of hemoglobin with oxygen.

Let's observe separately such aspect of circulatory system modeling as hemorrhagic shock. Concerning this the small review [115] attracted our attention; where seven mathematical models of hemorrhagic shock were analyzed. The authors noted that although the mathematical modeling of pressure and flow dynamics in cardiovascular system had long history, finding an appropriate model for particular experimental situation was often a challenge by itself. The ideal model should be relatively easy to use and reliable, as well as ethically acceptable. In addition, it would help the pathogenic features of cardiovascular diseases that need to be investigated. No universal model had been identified, although many models had been developed. The purpose of the review was to describe several of the most relevant mathematical models of the cardiovascular system: to explain the physiological features of the dynamics of blood circulation and to compare their mathematical formulations. The focus was on whole-organism mathematical models that map the subject's response to hypovolemic shock. The models contained in this review differed from each other both in the accepted mathematical methodology and in described physiological or pathological aspects. In fact, each model mimics different aspects of physiology and pathophysiology of cardiovascular system to varying degrees: some of these models were aimed to better understanding of the mechanisms of vascular hemodynamics, while others focus more on disease states in order to develop therapeutic standards of care or test new approaches.

Continuation of these problems studying one can find in [116]. Hemorrhagic shock is the leading reason of the deaths of militaries on the battlefield as well as civilian injuries. This article presents an updated version of Zenker model (2007) for hemorrhagic shock, called the ZenCur model, which allows better description of the time course of phenomena relevant observations. The study provides a simple but realistic mathematical description of the dynamics of cardiovascular system, which may be useful in estimation and predicting of hemorrhagic shock. This model was able to reproduce changes in mean arterial pressure, heart rate and cardiac output after the beginning of bleeding (as observed in four experimental laboratory animals). It provided a reasonable compromise between too detailed description of relevant mechanisms, on the one hand, and the simplicity of the model, on the other. The first one was required significant modeling and entail cumbersome interpretations. From clinical point of view, the goals of new model were to predict survival and optimize the timing of therapy in both civilian and military scenarios.

Finally, an article [117] two different cardiovascular models in hemorrhagic shock scenario were compared. Hemorrhagic shock is a form of hypovolemic shock caused by rapid and large loss of intravascular blood volume and is the world's leading cause of death, whether on the battlefield. or in civil traumatology. For this reason, the ability to prevent hemorrhagic shock remains one of the largest challenges in medicine and technology. The use of mathematical models of cardiovascular system had expanded the possibilities: on one hand, for predicting the risk of developing hemorrhagic shock, and, on other hand, for determining effective treatment tactics. This article presents material of comparison between two mathematical models that model multiple hemorrhagic scenarios. Guyton and Zenker models were observed. In the vast panorama of existing mathematical models of cardiovascular system, we decided to compare these two models because they seem to be extreme cases due to their complexity and details of information they analyze. The Guyton model is complex and well-structured model that represents a milestone in the investigation of cardiovascular system; the Zenker model is newer, developed in 2007, and it is relatively simple and easy to implement. Comparison of these two models opens us new prospects for improving of mathematical models of cardiovascular system, which may be more effective in the study of hemorrhagic shock.

Thus, the development of mathematical models of physiological processes in healthy organism at rest and under various disturbing influences is rapidly developing area of mathematical modeling. At the same time, numerical simulation seems to be exceptional in terms of its efficiency and availability of tools for studying the problems of physiology and medicine. An analysis of literature has shown that the complexity and detailed elaboration of physical and mathematical formulations of the problems in modern conditions is directly related to the rapid growth of computing resources, and the revolution in the field of instrumental and diagnostic equipment plays significant role too, providing penetration to fundamentally new levels of understanding of the processes occurring in human organism. At the same time, modern invasive methods, no matter how perfect they are, give only some "slice" of the current state of a person, while in modern society, in particular, in occupational medicine and sports, there is a request to predict the functional state of a person under the certain or other extreme disturbing influences. In addition, there is a gap between works in which the fundamental scientific component comes to the fore and works that can be used in real time to solve applied problems in medicine and physiology.

Summarizing all above written, it can be argued that the proposed models require the use of rather complex mathematical apparatus and significant computational resources. In addition, they were not always justified from mathematical point of view, they were based on a number of significant limitations, and there were also issues of checking the adequacy of such models. In particular, the adequacy of such models was checked by comparative analysis of the temporal implementations of the models and data from natural experiment in healthy subjects and patients. Therefore, the scope of their application seems to be rather limited, there are certain difficulties in the practical application of such models associated with obtaining of input data. In addition, such models, at least some of them, although they were parts of more complex formations, it was not clear how they took into account the interaction and mutual influence with other functional systems of organism. At the same time, there was specific request for mathematical models on which it would be possible to study the processes occurred in human organism at the level of predicting the stationary state of organism during disturbances of various etiologies, the input data for which would be obtained from experiment.

The emergence and development of models of individual oxygen transport systems of organism naturally led to the consideration of their interconnected holistic functioning, united by common task — to ensure an adequate supply of oxygen to organism. In this regard the concept of Profs. A. Z. Kolchinskaya and N. V. Lauer about oxygen regimes of organism and mechanisms of their regulation were formulated in time [17]. Based on the analysis of large amount of experimental data, they had concluded that the regulation of oxygen regimes of organism was carried out by single system that coordinates the most complex work of wide variety of mechanisms and subordinates them to the main task of maintaining of oxygen parameters at optimal level throughout the entire path of oxygen in organism — for the most economically, efficiently, effectively, and reliably matching of oxygen delivery to tissue in accordance to demands in oxygen.

This approach is currently in demand. In particular, automated workstations for functional diagnostics were developed [ta 2019Ak], in [Masha],

Basing on this concept, a simulation model of the dynamics of gases in organism was developed, which described the mass transfer of respiratory gases in human organism by all oxygen transport systems in the dynamics of respiratory cycle [22, 23]. Regulation in the system is carried out according to the principle of the optimal choice of control parameters (respiration volume, duration of respiratory cycle, volumetric velocities of systemic and regional blood flows), i.e., the problem of regulation was formulated as classical optimization problem according to given criterion, which is the minimum squared deviation of O_2 delivery value from oxygen request. The model was used to study the dynamics of respiratory gases mass transfer in organism under the conditions of hypoxic hypoxia, physical activity, and hyperbaria [24–26]. Transient processes were studied during changes in the composition of inhaled air, as well as for the transition from the rest to exercise — so, conversely, pressure changes, and the process of controlling the level of gas homeostasis in organism. A qualitative analysis of the model was carried out: the existence and uniqueness of solutions, non-negativity, boundedness, and asymptotic stability were demonstrated. This model was used to solve a number of applied problems of occupational medicine and sports.

Currently, there are two main approaches to mathematical modeling of respiratory and blood circulatory systems. One of them was the construction of models for the mechanics of respiration and blood circulation, which were based on models of mechanics of rigid solid deformable objects, thermomechanics, hydromechanics, and continuum mechanics. This approach supposes using of complex mathematical apparatus, including Navier-Stokes equation, which makes it possible to obtain a number of theoretical results, but it is hardly possible for real problems solutions today. The second approach was based on the model of F. Grodins, who imagined the process of the breath as controlled dynamic system, described using ordinary differential equations, in which the control was carried out according to the feedback principle. There are significant numbers of modifications of this model, which make it possible to simulate various disturbing influences, such as physical activity, hypoxia and hyperemia, and to predict the parameters characterizing the functional respiratory system under these disturbing influences.

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МАТЕМАТИЧНІ МОДЕЛІ СИСТЕМИ ДИХАННЯ І КРОВООБІГУ

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Метою цієї роботи було проаналізувати сучасні підходи до математичного моделювання системи дихання та кровообігу.

Методи. У якості методів були використані комплексний аналіз та огляд літератури з використанням вітчизняних та зарубіжних баз даних.

В результаті виконаної роботи в огляді було узагальнено та проаналізовано історичні відомості та сучасні дані, що стосуються математичного моделювання функціональних систем дихання та кровообігу, виявлено сучасні тенденції у підходах до побудови цих моделей.

Висновки. В результаті необхідно зроблено висновки про те, що в даний час існує два основних підходи до математичного моделювання систем дихання та кровообігу. Один з них — це побудова моделей механіки дихання та кровообігу, що ґрунтуються на моделях механіки твердого деформованого тіла, термомеханіки, гідромеханіки, механіки суцільних середовищ. Цей підхід передбачає застосування складного математичного апарату, зокрема й рівняння Нав'е-Стокса, що дозволяє отримати низку теоретичних результатів, але навряд чи він є можливим нині для вирішення реальних завдань. Другий підхід полягає в моделі Ф. Гродінза, який представив процес дихання як керовану динамічну систему, записану за допомогою звичайних диференційних рівнянь, управління у якій здійснюється за принципом зворотного зв'язку. Існує значна кількість модифікацій цієї моделі, які дають можливість імітувати різні збурювальні впливи, такі як фізичне навантаження, гіпоксія, гіперкпнія й спрогнозувати параметри, що характеризують функціональну систему дихання при цих збурювальних впливах.

Ключові слова: математична модель дихальної системи; математична модель системи кровообігу; гіпоксичний стан; теоретичний аналіз.