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ADVANCES IN HUMAN PHYSIOLOGY RESEARCH

Volume 4·Issue 1·June 2022 ISSN 2810-9805(Online)

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Volume 4 Issue 1 · June 2022 · ISSN 2810-9805(Online)

Advances in Human Physiology Research

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EDITORIAL

Extracellular Vesicles and Their Significance in COVID-19

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ARTICLE INFO

Article history
Received: 25 April 2022
Accepted: 05 May 2022
Published Online: 18 May 2022

Over the last few years, there is huge scientific attention towards the research related to Extracellular Vesicles (EVs), because of their unique property of inter cellular communications and effective biological significance in diagnosis and therapy [1]. Extracellular Vesicles are lipid bilayer membrane bound biological entity, which contains different bioactive compounds (cargoes) such as microRNAs (miRNAs), mRNAs, proteins, and lipids. Based on their origin and size, EVs have been categorized into three different types (a) Exosomes (40 nm-150 nm) are smallest EVs, which are synthesized by endocytic pathways in the cells and secreted in extracellular space through exocytosis process, (b) Microvesicles are secreted from direct budding off plasma membranes and their size varying from 50 nm to 1000 nm and, (c) Apoptotic bodies are formed during apoptotic cell death process and respectively larger in size > 1000 nm [1-3]. EVs have been identified using different markers, that includes tetraspanins proteins (CD9, CD63, CD81, and CD83), endosomal sorting complexes required for transport (TSG101, Alix), heat shock proteins (Hsp60, Hsp70, Hsp90), and Rab proteins (RAB27a/b) [1].

EVs have been considered as key transporters of cargoes for intercellular communication by passing

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DOI: https://doi.org/10.30564/ahpr.v4i1.4661
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signals from one cells to neighbour or remote (target) cells to regulate their physiological process. In pathological conditions, the quantity of EVs and their molecular cargo varies as compared to normal cells. In such condition, EVs may remodel the target cell by affecting the immune cells, consequently could regulate cell proliferation and migration in cancer and other diseases via enhancing inflammation [4], that depicts their role in pathogenesis of various diseases such as cancer, diabetes, cardiovascular, neurodegenerative and kidney disease [5]. In latest COVID-19 pandemic disease, EVs has been associated with dual role in both pathogenesis and therapeutics. Researcher reported that EVs derived from virus infected cells modulate the immune system of the host, leading to increase in the rate of viral load [6,7]. Recent studies have demonstrated that the structures of SARS-CoV2 and EVs are very similar. Therefore, it was hypothesized that SARS-CoV2 might exploit EVs to get exit from the cells; whereas EVs may use virus penetration mechanism for the delivery of their cargoes. Hence, the concept of interaction between virus and EVs could be employed for the development of vaccines and drug against COVID-19 management [8]. EVs have been also associated in enhancing the lung immunity and it is well known that lung is most affected organs in COVID-19, hence EVs might be very useful in repairing lungs during COVID-19 infections [9].

Therapeutic Potential of EVs for COVID-19

Mesenchymal Stem Cells (MSCs) were known for their therapeutic utilities in the treatment of various diseases, because of their potential regenerative and immunomodulatory properties. The numerous research studies have demonstrated that MSC-derived EVs perform similar role to their origin of cells i.e., MSCs, suggesting that therapeutic potentials of MSCs in various diseases are mainly performed by their secreted EVs [1]. Studies have suggested that both EVs and MSCs have anti-inflammatory and immunomodulatory properties, which might supress developing edema in lungs [1]. Hence, EVs derived from MSCs have drawn great scientific attention for their therapeutic utilities as a cell-free therapy for various diseases.

EVs were assumed to be involved in the treatment of COVID-19 disease via delivering their immunomodulatory and anti-inflammatory microRNAs (miRNAs) and proteins to infected or activated alveolar cells in lungs [10-12]. It has been reported that EVs carry various types of miRNAs such as let-7, miR-124-3p, miR-21-5p, miR-146a and miR-145. Of which, miR-124-3p was associated with the suppression of oxidative stress and inflammatory cytokines through interaction of its receptor P2X ligand-gated ion channel 7 (P2X7) [10]. Also, it has been demonstrated that there is huge production of inflammatory cytokines, leading to cytokines storm and lung damages during COVID-19 infection. Another miR-21-5p of EVs has been linked with reduced apoptosis of lung cells by inhibiting PTEN and PDCD4, whereas miR-146a were involved in transformation of pro-inflammatory macrophages to anti-inflammatory condition using suppression of NF-κbsignalling pathway [10]. In last, miR-145 of EVs have been reported to enhance the phagocytic capacity of macrophages for quick and speedy removal of pathogens in respiratory tract and lungs [13]. Hence, these miRNAs of EVs could be utilized as potential therapeutic molecule against COVID-19. However, our knowledge on these EVs is very limited, and more experimental works are much needed to make sure their therapeutic potential to combat COVID-19 pandemic.

EV-Based Vaccines for COVID-19

EVs have been known for various properties such as highly stable, less toxic, and low-immunogenicity, which make them a potential biological entity in developing vaccines against COVID-19 [14]. Currently, vaccines are very promising in preventing SARS-CoV-2 infection in humans all over the world. As of now, various vaccines are being utilized to enhance immunity against SARS-CoV-2, which saved huge population from death worldwide [14]. Till date, lipid nanoparticles have been considered as a good carrier for vaccine development against COVID-19. Many vaccines utilized nanoparticles, which encapsulated mRNAs-1273 (BNT162b1, CVnCoV) and saRNAs (LNPn CoVsaRNA) and have been given to human population as a preventive measure for COVID-19 infection in different regions including Germany, Belgium, and the United States [15]. As a naturally biological nano-vesicles, EVs may be an alternative novel source of carrier in developing vaccine to combat with this deadly pandemic [16,17]. Vaccines utilizing EV carry SARS spike proteins and its efficacy was checked and compared with adenoviral vector vaccine. Both types of vaccines (EV-vaccines and adenoviral vectors) have shown promising results in neutralizing antibodies at the same level. Later, maximum level of antibody reutilization was achieved when combination of both adenoviral vector and EV based vaccine was assessed, which was higher than the convalescent serum of SARS patients [18].

EVs were reported to bind with immune cells and activate immune reactions, which helps in recognition and neutralization of specific types of cells [19]. Also, EVs have been shown to have a greater efficiency than

that of soluble proteins which are utilized in vaccine development. This property might contribute in producing higher copies of the same viral protein, resulting into enhanced cross-linking of EVs and B-cell receptors [20]. These pieces of evidences suggest that EVs carrying SARS-CoV-2 components might be very useful in developing COVID-19 vaccine.

Conclusions

In spite of multiple treatment methods such as drugs and vaccines applied for overcoming COVID-19 pandemic, a multidirectional strategy must be established to reduce the pervasiveness of SARS-CoV2. Even after getting multiple dose of vaccines, people have been tested positive for COVID-19, and their symptoms got severe and worsen. Therefore, in order to treat the severe cases and prevent aggravassation, Extracellular Vesicle (EVs-Exosomes and Microvesicles) therapy might be a potential alternative therapeutic choice. As EVs has been known to have immunomodulatory, regenerative, and antibacterial properties, which might contribute to COVID-19 therapy. Based on these evidences, EVs might be utilized as a cell-free therapy and as a natural drug delivery vehicle in COVID-19 management.

Acknowledgment

Sanjay Kumar would like to thanks Sharda University for all the resources.

Conflict of Interest

There is no conflict of interest.

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Advances in Human Physiology Research
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ARTICLE

Modeling of Mechanisms Providing the Overall Control of Human Circulation

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ARTICLE INFO

Article history
Received: 31 May 2022
Accepted: 21 June 2022
Published Online: 05 July 2022

Keywords:
Arterial pressure
Angiotensin
Baroreflex
Chemoreflex
Hypertension
Renin-angiotensin systems
Ischemia
Simulation

ABSTRACT

Multiple humoral and nervous mechanisms, each influencing the cardiovascular system (CVS) with its specific dynamics and power, had been evolutionarily saved both in animals and in human organisms. Most of such mechanisms are considered to be controllers of CVS's function, but there is no concept clearly explaining the interaction of global and local controllers in intact human organisms under physiological or pathological conditions. Methodological and ethical constraints create practically insuperable obstacles while experiments on animals mainly concern artificial situations with certain switched-of mechanisms. Currently, mathematical modeling and computer simulations provide the most promising way for expanding and deepening our understanding of regulators' interactions. As most of CVS's models describe only partial control mechanisms, a special model (SM) capable of simulating every combination of control mechanisms is encouraged. This paper has three goals: i) to argue the uncial modeling concept and its physiological basis, ii) to describe SM, and iii) to give basic information about SM's test research. SM describes human hemodynamics, which is under influence of arterial baroreceptor reflexes, peripheral chemoreceptor reflexes, central (cRAS) and local (lRAS) renin-angiotensin systems, local ischemia, and autoregulation of total brain flow. SM, performed in form of special software (SS), is tested under specific endogenous and/or exogenous alterations. The physiologist using SS can easily construct the desirable configuration of regulator mechanisms, their actual state, and scenarios of computer experiments. Tests illustrated the adequateness of SM, are the first step of SM's research. Nuances of the interaction of modeled regulator mechanisms have to be illustrated in special publications.

1. Introduction

Ideas about mechanisms that regulate the state of the cardiovascular system (CVS) have undergone a certain evolution. For a long time, the concept of prevailing nervous regulation of the pumping function of the heart and the tone of regional vessels dominated. In particular, arterial baroreceptor reflexes (ABR) are supposed to be

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DOI: https://doi.org/10.30564/ahpr.v4i1.4763
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the main mechanism that minimizes perturbations of the mean arterial pressure (MAP) despite regular violations of arterial pressure in each cardiac cycle [1-3]. In addition, MAP is under regulator influences of chemoreflexes (CHR): at least, it is well-known that alterations of blood pH, PaCO2, and PaO2 activate peripheral chemoreceptors located in specific bulbs of the aortic arch and carotid sinuses. Both CVS and lung ventilation are under CHR. Central (cRAS) [4] and local (lRAS) renin-angiotensin systems are considered the main humoral mechanism capable of essential elevation of MAP [5-7].

The long-term trends of MAP were and remain in the focus of clinicians too [8]. In order to clarify whether MAP's shifts like chronic hypertension or hypotension have a compensatory or pathologic origin, clinicians need an adequate concept explaining the mechanisms of these shifts. But special investigations have shown that ABR and CHR are not responsible for the long-term level of MAP [5]. Therefore, by the mid-1960s, the special concept of neurohumoral regulation of MAP came to the fore [4]. The key point of the concept is the involvement of renal mechanisms ensuring blood water-electrolytic homeostasis. Further exploring these main concepts over time revealed nuances supporting the thought that the overall control of CVS is likely tricky. Currently, despite the intensive research on multiple aspects of arterial hypertension (AH), neither physiology of CVS nor the origin of its pathology is completely understood. At the same time, the current fight against secondary AH is aimed at reducing the influences of CNS and local humoral mechanisms on MAP's three main determinants (total blood volume, heart pumping function, systemic vascular compliance, and resistance). Clarifying of real roles of these three characteristics of CVS could help a computer model (CM), that describes the functions of mechanisms regulating CVS, and that is properly realized as special software (SS).

The purpose of the paper is to present to readers: i) the uncial modeling concept and its physiological basis; ii) a description of CM; iii) basic information about SS and the main results of test simulations.

2. The Modeling Concept and Its Physiological Basis

Models of CVS assisting both physiologists and physicians have been proposed since the 1960-s. Initially, models were relatively simple and concerned those fragments of CVS, biophysical characteristics that had been properly estimated or well-measured [10-16]. The modeling of CVS's most fragments did not require such physiological nuances as hemodynamic effects of local or organism-scale control mechanisms. Their modeling was the next step. The main approaches to modeling CVS's controllers are presented in the review [9].

Usually, the modeler tried to formalize the concept created by physiologists on a basis of experiments. By this, the model should have been analyzing and clarifying certain quantitative aspects of the concept. I do not know any model used to prove a novel conceptual hypothesis. The complex model created by Arthur Guyton with coauthors and tried to understand the main regularities of circulation control was the exclusion [4]. So, modelers mainly described the acute effects of ABR. The hemodynamic aspect of CHR was taken into account rarely and in the assumption that these reflexes and ABR act additively [9]. But this assumption, which seemed to be obvious, is not correct for the entire diapason of reflexes. If more detailed, even for baroreceptor reflexes activated from receptors of the aortic arch and carotid sinuses, the additivity was observed only for moderate changes of transmural pressures in these zones of ABR. Already in the model, created for simulating human hemodynamic responses to +Gz accelerations [13], it was revealed a specific phenomenon: under extreme values of acceleration, the carotid reflex and aortic reflex function antagonistically. This observation has been explained [17]. Besides, this fact prompted us to assume that different control mechanisms, which evolutionarily appeared either in different organs or in the same organ at different times, may have their own local (organ-scale) useful effects [18-22]. Further thoughts transformed this assumption into a belief that most organ-scale control mechanisms are conserved through evolution due to their positive role in the survival of the organ [23]. If more detailed, the functions of the organ, critical for the organism's survival, is closely correlated with the number of organ's specialized cells. Namely, the physical integrity of each cell is the necessary condition for its output functions. Dynamic colonies of different types of cells are constructive elements of multicellular physiological chains. In particular, such chains form multicellular physiological regulators. So, the correlation between the current level of chain function, on the one hand, and cells' current functionality in each colony, on the other hand, is the fundamental determinant of their current state. Depending on the number of cells synchronically reacting to altered input variables, the level of the output function varies. This explains both the mechanism of physiological fluctuations and their crucial role in integrative physiology (IP) [21-23]. Here I would special stress that these background factors determine IP even under human rest conditions. So, individual values

of life indicators (body temperature, arterial pressure, e.a.) are determined both by genetics and the current states of organs and systems providing cell metabolism. Namely, these microscopic events are "the clue" functionally integrating intracellular physiology with the physiology of the entire organism. The novel understanding of IP clarified the real role of both CVS and its so-called controllers in the human organism. In particular, this view presented [22-24] as a general concept of optimal circulation, is our modeling concept.

According to this concept, under stagnated metabolism cells produce interim chemicals including those directly or indirectly modifying certain cardiac and (or) vascular parameters until the metabolism is not recovered. These chemicals often denoted by the term factors of adaptation (FA) may have different molecular weights. The low-molecular-weight FAs predominantly act locally: by penetrating into a cell nucleus, they can modify the expression of those genes that are associated with mitochondria, and govern their proliferation and hypertrophy. This is the main way of adapting the cell to its altered mean rates of ATP consumption. Additionally, other parts of FAs left the stagnated cell, and with blood flows reaching certain target cells, activate the function of organs-providers of cells by oxygen and nutrients. In particular, local vasodilation of stagnated organs is one of the effective and speed-acting ways of for compensating the lack of ATP and overcoming of organ's lowered metabolic rate. In the light of this idea, well-known humoral control mechanisms like cRAS and lRAS are considered by us negative feed-backs trying to provide optimal-like organ-scale circulation via constricting of arterioles in all organs. Despite the vasculature of the organ initiated this constriction also is under vasoconstriction, the general protective effect is in increasing of organ's inflow. So, both cRAS and lRAS should be modeled in the same way. Depending on cell localization, the effects of their FA may be organ-scale, regional, or global. Namely, these nuances determine scales and the power of resulting hemodynamic manifestations.

Along with this type of humoral controller of hemodynamics, there are nervous-reflector mechanisms that also may act at local, regional, and organism scales. Some of these control mechanisms are better studied than others. It is not excluded that some mechanisms are still unknown yet. Important is that one and the same cardiovascular parameter may simultaneously be under influence of more than one FA. As every real biological parameter has a limited range of its alterations, reasonable is the assumption that the excess concentrations of FA (or excess nervous impulses) do not have additional effects. In other words, the maximal effect is limited thus the algebraic additivity of all applied efforts will take place only for low or up to moderate single efforts.

Under conditions of the physiological norm, a maximal number of cells will be provided by their current comfort metabolism without the stress of control mechanisms. Certainly, different types of cells have different mean rates of metabolism. Besides, in every specialized cell, this rate is not stable but is altered in different phases of a cell cycle. These genetically predetermined alterations do form organism-scale variable demands of nutrients. Therefore, activities of every organ participating in the forming of nutrients' actual concentrations in arterial blood, as well as the functional state of CVS providing the transport of these nutrients to their end-users, must be properly self-adapted to the needs of cells both at the organism-scale and in organs-scales.

To clarify the impact of this general view of IP, it useful is to shortly recall two main concepts of the goal function of CVS. Traditional cardiovascular physiology established that CVS provides organism by two variables – cardiac output (CO) and cyclic variations of arterial pressure (AP). At the cell scale, physiology is mainly dependent on local capillary pressure (CP). Its mean value depends on the mean arterial pressure (MAP). On the other hand, although the function of ABR is based on alterations of AP, namely the relative stability of MAP guaranties the stability of CP. Moreover, there is no special controller of CO. This short argumentation already creates a basis to conclude: that CVS neither has its own specific goal function nor mechanisms for setting and regulating the long-time level of MAP.

All said above prompts that multiple organs, directly or indirectly involved in the complex process maintaining of cells' adequate metabolism, are controllers (most correctly, modifiers) of the activity of these organs. From the energy point of view, the total expenditure of ATP is minimal when cells are materially provided without additional activation of nervous mechanisms. In other words, every organ is default tuned to provide the optimal metabolism of its cell. In rest conditions, the vegetative nervous system, via *truncus sympathicus* and *nervous vagus* influences the heart function, and via *truncus sympathicus* altering the tonus of vasculature, and provides an optimal-like organism-scale metabolism. In this, CVS has its role that is reciprocally dependent on the activity of those organs that provide the arterial blood chemistry. Every exogenous or endogenous factor increasing the rate of molecular destruction disturbs this ideal cellular life. To recover the balanced metabolism,

additional modulations of the functionality of both CVS and these assistant organs must be provided. Namely, both the vegetative nervous system and multiple local controllers of organ circulation are the mechanisms integrally optimizing cell metabolism. Certainly, these regulator efforts create both acute fluctuations and long-term trends in hemodynamics. Namely, this is the platform on which our models are created. As there are parallel ways of moderating this activity, the final effect always is a function of time. In order to correctly model this effect, the modeler has to use differential equations that describe both the hemodynamics in the vascular net and the dynamic influences of associated mechanisms modifying parameters of CVS. Indeed, the required model becomes rather complex.

3. The Conceptual Scheme of the Complex Model

A conceptual scheme of our complex model is depicted in Figure 1. A red color rectangle depicted in the center of Figure 1 represents the core model describing hemodynamics in a lumped parametric CVS. Theoretically, the parameters of this model can be either fixed or dynamically altered. Under the fixed values of blood volume, heart rate, ventricles' inotropic state, as well as compartmental vascular characteristics, the model of CVS simulates hemodynamics in a hypothetic case when none of the neural-humoral regulators is working. In versus cases, the model of CVS simulates hemodynamics under switched-on one or more regulators. Namely, by means of switching on or switching off (these procedures are accessible via a special user interface (UI)) the chosen combination of regulators, the user (physiologist-researcher) is capable of simulating every desired configuration of endogenous mechanisms. In addition, the UI provides the user with opportunities to create scenarios for executing a computer experiment (namely, simulation) and analyzing its results that represent the dynamics of both input and output variables.

In Figure 1, figurate arrows like ↱ special indicate that the corresponding model also has direct inputs provided by UI. Combinations of multiple arrows illustrate that values of associate input or output flow can be directly modulated by means of UI. These temporarily implemented additional options have been used to provide first (rough) assessments concerning the likely contribution of real mechanisms modulating these flows in the intact organism.

The additional two blocks at the top part of the picture reflect our attendance to develop an advanced version of the model capable of simulating both main hypotheses

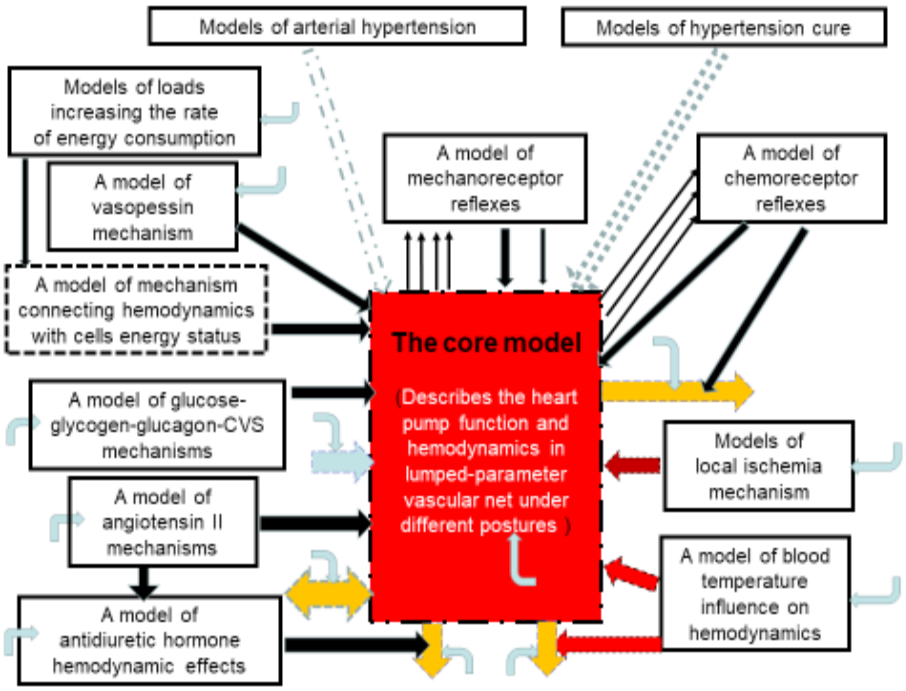

Figure 1. Schematic illustration of the core model (representing hemodynamics in a vascular net) with ten mechanisms permanently modifying its parameters. Figurate arrows conditionally show that every modifier in turn is under influence of dynamic endogenous and/or exogenous physiochemical factors.

concerning mechanisms of arterial hypertension and technics of its cure.

4. Mathematical Models

The complex quantitative mathematical model schematically depicted in Figure 1, is the basis of special software (SS) providing computer-based simulation research of human circulation. According to this scheme, the model of human CVS working as an open system interacting with a certain number of associated physiological systems (APS) is the core model. Within the framework of traditional physiology, several of these APS are known as circulation controllers. They are capable to alter the total blood volume and current values of CVS's parameters. In case these controllers are switched off, the model will describe hemodynamics in uncontrolled CVS.

4.1 A Short Description of the Core Model

Our models are dynamic. The core model uses the most spread approach of lumped parameters [10,14]. It is worth stressing here that the core model of hemodynamics contains two sub-models separately describing pump functions of the right and left ventricles respectively. The third sub-model describes hemodynamics in a vascular net of 21 lumped-parametric arterial and venous compartments. Each vascular section possesses its own constant initial characteristics (rigidity, unstressed volume, and resistance between neighboring lumped-parametric vessel sections). In addition, the core model assumes the total blood volume is constant. But in the complex model, the total blood volume is under influence of certain endogenic mechanisms. Namely, each of the so-called control mechanisms is able to alter the value of at least one of the cardiovascular parameters included in the core model.

Both ventricles are modeled similarly to a flow generator: it connects the mean output flow of ventricles with their constant parameters and variable mean input pressure. The transforming function of the ventricle takes into account the ventricle's structurally determined constants, as well as its inotropic state. The stable heart rate on its autonomous level transforms ventricles' output to a heart output in ml/sec. So, the heart model does not imitate cardiac pulsatile behavior but is a model relative to mean values of pressures and flows.

In our complex model, main simulations do cover long time periods (tens of minutes, hours, and days), thus the pulsatile model of a heart pump function (HPF) is substituted by the model describing HPF as a generator of mean blood flow.

4.1.1 Heart Pump Model for Simulation of Quasi-static Hemodynamics

Under simulating long-term processes in CVS using standard PC, experts often meet a lack of computing resources. There are two main ways for solving this problem: 1) reducing the model of CVS; 2) using special algorithms that organize regular freeing up computer RAM by saving portions of current information on external memory. Both these strategies have been used by us. Instead of a pulsating heart, this version of the heart pump model (HPM) operates with constant values of cardiac output (Q), mean heart rate (F), inotropic coefficient (k), elasticity (C_v), free filling volume (U_v), and mean pressure value (P_f) filling the ventricle in diastole. HPM looks like:

$$Q_i(t) = \frac{F(t)\cdot k_i(t)((P_{fi}(t)\cdot C_{vi}(t) + U_{vi}(t)) - U_0)\cdot(1 - A_i(t))}{1-(1-k_i(t))A_i(t)}$$

$$A_i(t) = e^{-(\tau_d / r_1 \cdot C_{vi}(t))}$$

$$T_h(t) = 60/F(t)$$

$$\tau_d = \alpha \cdot T_h(t) + (1 - k_i(t))\cdot\beta$$

$$V_{si}(t) = Q(t) * T_h(t)$$

$$k_i(t) = (V_{si}(t) + U_{0i})/V_{ed}(t)$$

$$V_{ed}(t) = (V_{si}(t) + U_{0i})/k_i(t)$$

$$P_i(t) = \begin{cases} 0, V_i(t) < U_i \\ (U1_i - U_i)/C_i, U_i \le V_i(t) \le U1_i \\ (U1_i - U_i)/C_i + (V_i - U1_i)/C1_i, V_i(t) > U1_i \end{cases} \quad (1)$$

$$R^K_{aV}(t) = \begin{cases} r_1, \Delta P_K(t) > P_{KP} \\ r_2, \Delta P_K(t) \le P_{KO} \end{cases}$$

$$V_i(t) = V_i(0) + \int_0^t (Q^I - Q^O)dt$$

In equation system (1), low index $i = \overline{1,2}$, where $i = 1$ -for the right ventricle, and $i = 2$ - for the left ventricle, $T_h(t)$ - duration of a cardiac cycle, α and β – are approximation constants, r_i – hydraulic resistances of ventricles' input valves.

The system (1) is the basis for simulating alterations of the heart pump function under changes of input pressures $P_{It}(t)$ for fixed values of $C_{vi}(t)$ U_{vi} and U_{0i}.

4.1.2 The Model of Hemodynamics in a Vascular Net

In every vascular compartment, by analogy with heart chambers, nonlinear dependences between blood pressure ($P_i(t)$) and volume ($V_i(t)$) is calculated using three current variables: $V_i(t)$, unstressed volume ($U_i(t)$), and the compartment's rigidity ($D_i(t)$):

$$P_i(t)=\begin{cases}0, V_i(t)<U_i(t)\\ (U1_i(t)-U_i(t))\cdot D_i(t), U_i(t)\le V_i(t)\le U1_i(t)\\ (U1_i(t)-U_i(t))\cdot D_i(t)+(V(t)_i-U1_i(t))\cdot D1_i(t), V_i(t)>U1_i(t)\end{cases}, \quad (2)$$

where $U1_i(t)$, and $D1_i(t)$ are approximation parameters.

Blood flows $q_j(t)$ between *i* and *j* vascular compartments is calculated as:

$$q_{ij}(t)=(P_i(t)+\gamma\cdot H_i\cdot\sin(A_i(t))-P_j(t)-\gamma\cdot H_j\cdot\sin(A_j(t))/r_{ij}(t), \quad (3)$$

where $r_{ij}(t)$ is the hydraulic resistance between these compartments, *H* and *A*-their distance from the foot and angle relatively to the horizont. $r_{ij}(t)$ is calculated using an approximate formulae:

$$r_{ij}(t)\approx\begin{cases}r0_{ij}, V_i(t)\ge V0_i\\ r0_{ij}\cdot(V0_i/V_i(t))^2, V_i(t)<V0_i.'\end{cases} \quad (4)$$

where $V0_i=V_i(0)$, while $r0_{ij}$ and $V0_i$- represent compartmental volumes and resistances in conditions of physiological norm (the rest condition).

Alterations of $V_i(t)$ within a time step of *h* is calculated as:

$$V_i(t)=V_i(t-h)+\int_{t-h}^{t}(q_{ij}(t)-q_{ij}(t-h))dt. \quad (5)$$

Taking into account the exclusive role of the brain, the vascular model especially describes the dynamics of summary brain flow including its nervous origin auto-regulation within a certain diapason of pressure changes in cerebral arterioles $P^{CA}(t)$. The auto-regulation is provided through proper changes of resistance $R^{CM}(t)$:

$$\frac{dR^{CA}(t)}{dt}=\frac{\delta_M\cdot P^{CA}(t)-R^{CA}(t)}{T_m}, \quad P^{CA}_{min}<P^{CA}(t)<P^{CA}_{max}, \quad (6)$$

where δ_M is the time constant of this local mechanism. Out of the diapason $P^{CA}_{min}<P^{CA}<P^{CA}_{max}$, $R^{CA}(t)$ is described as:

$$R^{CA}(t)=\begin{cases}R^{CA}_{min}, P^{CA}(t)\ge P^{CA}_{max}; P^{CA}_{min}<P^{CA}(t)<P^{CA}_{min}\\ R^{CA}_{max}\cdot\left[1-\exp\left(X\cdot\left(P^{CA}(t)-P^{CA}_{max}\right)\right)\right], P^{CA}_{max}<P^{CA}(t)<P^{CA}_{max},\\ \frac{E_1}{P^{CA}(t)}, 0\le P^{CA}(t)\le P^{CA}_{min}\end{cases} \quad (6')$$

X and E_1 are approximation constants.

So, the extended system of Equations (1) – (6') represents the core cardiovascular model. It can be used as an autonomic model for simulating hemodynamics in a closed CVS under stable values of total blood volume, parameters of heart chambers, vascular parameters and given values of $F(t)=const$, and $k_i(t)=const$. In real organism, the core cardiovascular model becomes an object that may be under influences of APS. Therefore, to model events in intact organism or under partially functioning APS, their functions must be added to the core model.

4.2 A Short Description of Models of CVS's Controllers

Our models of cardiovascular control are based on concepts reflected [25-34]. AMP-associated mechanisms are formalized using ideas published in [35-38]. Several models are the advanced versions of the models proposed earlier [12,15-16,41-43].

Activities of efferent sympathetic ($E_S(t)$) and parasympathetic $E_V(t)$ nerves are under descending simulator ($E_{bS}(t)$) or inhibitor ($E_{bI}(t)$) influences of brain suprabulbar neuronal structures. Simultaneously, ascending receptions originated in body different structures (mechanoreceptors of CVS, muscles, peripheral chemoreceptors) modulate $E_S(t)$ and $E_V(t)$. At last, a wide range of endogenous chemicals, penetrated into the brain through circulation, also modulate $E_S(t)$ and $E_V(t)$. In this version of the model, dynamics of efferent sympathetic ($E_{Sh}(t)$) and parasympathetic ($E_{Vh}(t)$) heart nerves, as well as sympathetic vascular nerves ($E_{Sv}(t)$) are described as:

$$\frac{dE_{Sh}}{dt}=\chi_1\cdot E_S^{\max}-\chi_2\cdot N_{\Sigma B}(t)+\chi_3\cdot N_{\Sigma X}(t)+\chi_4\cdot E_{bs}(t)-\chi_5\cdot E_{bI}(t), \quad (7)$$

$$\frac{dE_{Sv}}{dt}=\lambda_1\cdot E_S^{\max}-\lambda_2\cdot N_{\Sigma B}(t)+\lambda_3\cdot N_{\Sigma CX\lambda}(t)+\lambda_4\cdot E_{bs}(t)-\lambda_5\cdot E_{bI}(t), \quad (8)$$

$$\frac{dE_{Vh}}{dt}=\mu_1\cdot E_V^{\min}+\mu_2\cdot N_{\Sigma B}(t)-\mu_3\cdot N_{\Sigma CX\lambda}(t)+\mu_4\cdot E_{bs}(t)-\mu_5\cdot E_{bI}(t), \quad (9)$$

where χ,λ,μ represent approximation constants, $N_{\Sigma B}$ is summary baroreception, $N_{\Sigma X}$ is summary chemoreception.

So, the complex model of the cardiovascular control must include at least those mechanisms that modulate vascular tonus and parameters of HPF. As the resistance depends on vascular volume (see (4)), it is necessary to describe summary ($m1$) nervous-humoral alterations of volumetric characteristics.

$$D(t)=D0+\sum_{i=1}^{m1}\Delta D_i(t); \quad U(t)=U0-\sum_{i=1}^{m1}\Delta D_i(t), \quad (10)$$

where *D*0, *U*0 represent the initial values of *D*(*t*) and *U*(*t*).

Within the interval $F_{\min}\le F(t)\le F_{\max}$, $F(t)$ should be calculated as:

$$F(t)=\begin{cases}F_{\min}, \sum_{j=1}^{n}\Delta F_i^-(t)>F_a-F_{\min}\\ F_a+\Delta F(T^o)+\sum_{i=1}^{m}\Delta F_i^+(t)-\sum_{j=1}^{n}\Delta F_i^-(t), F_{\min}\le F(t)\le F_{\max},\\ F_{\max}, \sum_{i=1}^{m}\Delta F_i^+(t)+F_a>F_{\max}\end{cases} \quad (11)$$

where F_a is the heart rate under normal blood temperature (T^o), biochemical characteristics of blood, and biophysical

characteristics of cells of sinus node, $\Delta F(T^o)$ is elevation of F_a with temperature increasing, $\Delta F_i^+(t)$ are accelerating effects of m mechanisms (including concentration of adrenalin) and $\Delta F_j^-(t)$ are retarding effects of n mechanisms.

Note that each mechanism forming its part of ΔF has its power and developmental inertia that have been taken into account by proper constants.

Inotropic states of ventricles are under influences of local coronary flows $q_c(t)$, adrenalin $A_d(t)$, T^o, $E_{Sh}(t)$, and $E_{Vh}(t)$. Special version of the model includes effects of exogenous cardio-active agents $C_a(t)$:

$$k_i(t) = k0_i * (1 + d_1 * (T^o(t) - T^o_N) + d_2 * (A_d(t) - A_{dN}) + d_3 * (q_c(t) - q_{cN}) + d_4 * (E_{cS}(t) - E_{cSN}) - d_5 * (E_{cV}(t) - E_{cVN}) \pm d_e * C_a(t)), \quad (12)$$

4.2.1 Mathematical Model of Arterial Baroreceptor Reflexes

To formalize the function of baroreceptor reflexes, it is necessary to create four sub-models adequately approximating all stages of ABR. The first sub-model represents the electrophysiology of the multi-fiber baroreceptor nerve $N_j(t) = f_a(P_j(t))$. The model must take into account both multiple zones of ABR and specifics of their activation thresholds and saturation pressures. The second sub-model represents the integration of these ascending pulse patterns with pulse patterns descending to the neurons of the solitary tract from the brain upper structures. The third sub-model must describe efferent modulations of the heart sympathetic and parasympathetic nerves, as well as regional changes of vascular sympathetic nerves. At last, the forth sub-model does describe nervous alterations of regional $U_i(t), U1_i(t), D_i(t)$, and $D1_i(t)$.

Assuming receptors' activity range to be between interval (0, 1), the nonlinear S-form functions of $N_j(P_j(t))$ are commonly presented as:

$$N_j(t) = \begin{cases} 0, & 0 \le P_j(t) \le P_j^* \\ \dfrac{1 - e^{\alpha_j (P_j^* - P_j(t))}}{1 + \beta_j e^{\alpha_j (P_j^* - P_j(t))}}, & P_j^* < P_j(t) < P_j^{**} \\ 1, & P_j(t) \ge P_j^{**} \end{cases}, \quad (13),$$

where $j = \overline{1,4}$ (reception zones of aortic arch, carotid sinuses, Willis circle, and lung arteries), α_j, β_j are constants, P_j^* is the local zone's activation threshold, P_j^{**} is receptors' saturation pressure. By altering values of α_j, β_j, P_j^*, and P_j^{**}, the user can simulate hemodynamic effects of $N_{\Sigma CX}(t)$ these receptor parameters.

It is assumed that at the nuclei of solitary tract, these four impulse patterns form an integral ascending signal.

$$N_{\Sigma B}(t) = \sum_{j=1}^{4} \rho_j \cdot N_j(P_j(t)), \quad (14)$$

4.2.2 Mathematical Model Describing Influences of Chemoreceptor Reflexes on CVS

Chemoreceptor reflexes have two effects – on lung ventilation, and on CVS. Assuming $N_{\Sigma CX}(t)$ to be the summary cheporeception, and $N_{CX1}(t), N_{CX2}(t), N_{CX3}(t)$- to be cheporeceptions concerned with $P_aCO_2(t), P_aO_2(t), pH(t)$ respectively, receptor's function is modeled as:

$$N_{\Sigma CX}(t) = N_{CX1}(t) + N_{CX2}(t) + N_{CX3}(t), \quad (14)$$

where

$$N_{CX1}(t) = 1 - Exp(\zeta_1 * (PaCO_2(t) - 40)) \quad (14')$$

$$N_{CX2}(t) = 1 - \omega * Exp(\zeta_2 * (7.4 - pH)); \quad (14'')$$

$$N_{CX3}(t) = 1 - -Exp(\zeta_3 * (PaO_2(t) - 99)); \quad (14''')$$

In last equations, ζ, ω- are approximation constants.

4.2.3 Mathematical Model Describing Hemodynamic Effects of Angiotensin II

In our current model, central and local renin-angiotensin-aldosterone mechanisms, acting through angiotensin II, represent negative feedbacks activated under lowered local blood flows in kidneys or other organs.

Real CVS is not an isolated system as it is assumed in the most models of hemodynamics. CVS interacts with multiple organs and anatomical-functional systems. In particular, total blood volume ($V_S(t)$), that is the main modifier of both central venous pressure and MAP, only in very little values of the observation time τ can be considered to be constant. Modifiers of $V_S(t)$ are acting via changing the liquid intakes from the digestive system ($q_w(t)$), of the diuresis ($q_d(t)$), expirations in lungs and skin. So, these effectors obviously do not belong to CVS.

$$\frac{dV_S}{dt} = q_w(t) - q_d(t) - q_{es}(t) - q_{ee}(t) - q_{cf}(t) + C_{be}(t) + C_{bl}(t), \quad (*)$$

where $q_{cf}(t)$ – trans-capillary flows, $q_{es}(t)$ – the evaporation with sweat, $q_{ee}(t)$ – expiratory fumes, $C_{be}(t)$- blood salt concentrations, $C_{bl}(t)$ - concentrations of blood lipids. The remained notations in (*) represent approximation constants.

Temporarily, it is assumed, that $V_S(t) = const$.

Vascular resistances $r_{ij}(t)$, calculated by (4), do alter via changes of $V_i(t)$, in turn associated with regional $U_i(t)$ $U1_i(t)$ $D_i(t)$ and $D1_i(t)$. Usually, the local inflow mainly depends on input pressure. So, the model of cRAS describes the dynamics of blood renin concentration ($R_{nk}(t)$)

in association with the critical value of pressure in kidney arterioles $P_{kc}(t)$ as:

$$\frac{dR_{nk}}{dt} = \begin{cases} \eta_k \cdot (P_{kc} - P_k(t)) - K_R & , P_k(t) < P_{kc} \\ -K_R & , P_k(t) \geq P_{kc} \end{cases}, \quad (15)$$

where η_k - sensitivity coefficient, K_R - time constant characterizing the velocity of renin utilization.

Assuming $R_{nh}(t)$ is $R_n(t)$ associated with heart local RAS, dynamics of $R_{nh}(t)$ is described depending on regional flow in coronary arteries ($q_c(t)$) as:

$$\frac{dR_{nh}}{dt} = \begin{cases} \eta_h \cdot (q_{cN} - q_c(t)) - K_R & , q_c(t) < q_{cN} \\ -K_R & , q_c(t) \geq q_{cN} \end{cases}, \quad (16)$$

Models of renin dynamics in brain $R_{nb}(t)$, liver $R_{nl}(t)$, and lungs $R_{nL}(t)$ are constructed by analogy with (9). The total concentration of renin $R_{nT}(t)$ in blood is calculated as:

$$R_{nT}(t) = R_{nk}(t) + R_{nh}(t) + R_{nl}(t) + R_{nL}(t) + R_{nb}(t), \quad (17)$$

The dynamics of blood concentrations of angiotensin II ($A_n(t)$) is modeled as:

$$\frac{dA_n}{dt} = \eta_{an} \cdot R_{nT}(t) - K_{an}, \quad (18)$$

where K_{an} is time constant characterizing the velocity of angiotensin II utilization.

4.2.4 Mathematical Model Describing Hemodynamic Effects of Local Ischemia

To imitate gradual ischemia of regional (kidney, coronary, or brain) artery, two parameters are used. One determines the magnitude ($\Delta_i^{\max}$) of local resistance's increase while the increase's speed is determined by the second parameter ($\Delta_i(t)$) as:

$$R_1(t) = \begin{cases} R_1 0 \cdot \left(\frac{V_i 0}{V_i(t)}\right)^2, & t < T_{bI} \\ R_1 0 \cdot (1 + \Delta_i(t) \cdot \left(\frac{V_i 0}{V_i(t)}\right)^2, & T_{bI} < t < T_{eI} \\ R_1(T_{eI}), & t > T_{eI} \end{cases}, \quad (19)$$

where $\Delta_i(t) = \Delta_i^{\max} \cdot (t - T_{bI})$,

Constants A, T_T, $\Delta_i^{\max}$, T_{bI} and T_{eI} will be set through UI.

4.2.5 Mathematical Model Describing Influences of Energy Lack to CVS

For correct understanding of mechanisms that determine MAP and origin arterial hypertension [9] principal is the question whether the human organism possesses by special mechanisms effectively coping with cell energy lack. If energy deficit mechanism (EDM) exists, it should work opposite to local intracellular and global energy lack. Intracellular acute mechanisms have been well discussed [34-36]. But the glucagon-glucose mechanism activating a back-transformation of liver glycogen to blood glucose is the main mechanism acting against organism-scale lack of ATP. Under glucose lack, glucagon, entering into blood, activates both the chronotropic and the inotropic states of the heart [24]. So, EDM has an additional opportunity to modulate the circulation. These modulations have been modeled for the first time as follows.

Taking into account that the physical activity of given dynamics $W(t)$ is the main originator of energetic problems, in our model blood glucose dynamics $G(t)$ is associated with $W(t)$ and dynamics of insulin $I(t)$ as:

$$T_G \frac{dG(t)}{dt} = G(t) + I(t) - \varpi_1 \cdot W(t), \quad (20)$$

Additional equation concerns dynamics of blood glucagon $g(t)$:

$$T_g \frac{dg(t)}{dt} = \begin{cases} \varpi_2 \cdot (G(t) - G_c) - g(t) - g_u, & G(t) \geq G_c \\ \varpi_3 \cdot (G_c - G(t)) - g(t), & G_c \geq G(t) \end{cases}, \quad (21)$$

In these equations, $G(t)$ and G_c represent current and critical blood glucose concentrations, $W(t)$ is the total load, $g(t)$ is the concentration of blood glucagon, ϖ_1, ϖ_2, and ϖ_3 are approximation constants, T_G and T_g characterize inertia of glucose-glucagon transformation mechanism.

$$\Delta k_g(t) = \varpi_4 \cdot (q_C(t) - q_C(0)); \; k(t) = k(0) + \Delta k_g(t);$$

$$\Delta F_g(t) = \varpi_5 \cdot q(t); \quad (22)$$

$$R_C(t) = R_C(0) \cdot (1 - \varpi_6 \cdot q_C(0) / q_C(t)), \quad (23)$$

Here again ϖ_4, ϖ_5 and ϖ_6 are approximation constants, $\Delta k_g(t)$ is the glucagon-caused increase of the heart inotropic state $k(t)$ from its initial value of $k(0)$. $q_C(0)$ $q_C(t)$ represent initial (normal) and current values of coronary blood flows, respectively, $R_C(0), R_C(t)$- represent appropriate resistances of coronary arteries. $\Delta F_g(t)$ is the glucagon-influenced acceleration of the heart rate.

4.2.6 Mathematical Models of Blood Temperature Influence on Hemodynamics

Blood temperature ($T^o(t)$) alterations ($\pm\Delta T^o$) alter almost linearly the heart rate $F(t)$ and regional vascular diameters. These effects have been modeled by us. In order to offer the user an access to these mechanisms, additional formulas describing activation (deactivation) of these mechanisms are needed. In our current SS, the incorporated formulas provide setting of numerical values of normal blood temperature (T_N^o) and stable velocity of temperature's elevation ($+v_T$) until the maximal ($T_{\max}^o$)

level is reached:

$$T^o(t)=\begin{cases} T^o_{\max}; & T^o(t)\geq T^o_{\max} \\ T^o_N+v_T\cdot t; & t_{bT}<t<t_{eT}; \end{cases} \quad t_{eT}=(T^o_{\max}-T^o_N)/v_T, \quad (24)$$

By analogy, under temperature lowering with stable velocity of ($-v_T$), and maximal ($T^o_{\max}$) or minimal ($T^o_{\min}$) levels:

$$T^o(t)=\begin{cases} T^o_{\min}; & T^o(t)\leq T^o_{\min} \\ T^o_N-v_T\cdot t; & t_{bT}<t<t_{eT}; \end{cases} \quad t_{eT}=(T^o_N-T^o_{\min})/v_T, \quad (25)$$

4.2.7 Mathematical Models of Input Loads

Our models and the entire SS imitate dynamic physiological responses of a healthy person to dynamic input loads. Namely, the response depends on the absolute level and shape of the applied load. Theoretically, it is possible to create a simulator providing the construction of every arbitrary load profile. Currently, our SS provides only fixed input loads each having its specific shape. At the same time, the shape is set based on the common trapezoidal shape formally describing the input load $W(t)$ as:

$$W(t)=\begin{cases} 0, & t<T_b; t>T_e \\ v_u\cdot(t-T_{p1}) & T_b\leq t\leq T_{p1} \\ W_{\max}; & T_{p1}\leq t\leq T_{p2} \\ W_{\max}-v_d\cdot(t-T_{p2}) & T_{p2}\leq t\leq T_e \end{cases}, \quad (26)$$

where $T_{p1}=T_b+W_{\max}/v_u$; $T_e=T_{p2}+W_{\max}/v_d$.

Here T_b is time to start the loading, T_{p1} - time when the maximum load $W_{\max}$ is reached; v_u is the load increasing velocity, v_d is the load decreasing velocity, T_{p2} is the end time of the load plateau, T_e is the exposure end time.

All other loads (changes of total blood volume, blood temperature, occlusion of local artery) have similar shape or its reduced versions.

Controlled linear alterations of total blood volume (V), namely ($\pm\Delta V$), are provided according to formulae:

$$\Delta V(t)=\begin{cases} V_{ab}(t)\pm v_{al}; & T_{b\Delta V}<t<T_{b\Delta V}\pm\Delta V/v_{al} \\ V_{ab}(t); & t\leq T_{b\Delta V}; t\geq T_{b\Delta V}\pm\Delta V \end{cases}, \quad (27)$$

where $V_{ab}(t)$ is abdominal vein volume, $T_{b\Delta V}$ is the start time for the altering of total blood volume with the velocity v_{al}.

Three human postures (horizontal, vertical, and sit) have been realized by giving proper fixed values of H_i, and A_i. To simulate the head-up tilt test on a chosen A, it is assumed every compartment to have the same $A_i=A$, and

$$A(t)=\begin{cases} A*t/T_T, & t\leq T_T \\ A, & t>T_T \end{cases}, \quad (28)$$

where T_T is the time for elevating the table.

So, the equation system (1)-(28) is the nominal mathematical model that can be used to simulate main cardiovascular responses to alterations of certain parameters of both endogenous and exogenous environments. To provide simulations, special software (SS) is created. To test partial models described above and to find out acceptable values of constants, special version of SS was used.

SS is too big to describe it here in detail. Procedures for both models configuration and simulation scenarios creation allow to simulate tens of thousands version of computer experiments. Currently, researchers of Bogomolets' Institute of Physiology of National Academy of Sciences (Kyiv, Ukraine) are testing SS. On a basis of these tests, it is planned to improve models, simulation scenarios, and SS. Before to describe and discuss results of test research, useful is to give brief information about SS.

5. About SS

As it was said, SS is a special software-modeling tool (SMT) that enhances the research potential of the physiologist via simulating a wide spectrum of events and situations that have ever been proposed as cardiovascular functional tests. The most known functional tests are:

1) Exogenous dynamic alterations of total blood volume;
2) Postural tests for different tilting angles;
3) Dynamic physical aerobic loads of given profiles;
4) Alterations of blood temperature;
5) Heart myocardium ischemia;
6) Brain ischemia;
7) Kidneys ischemia;
8) Shutdown of any number of control mechanisms (including the extreme case of the uncontrolled CVS).

In this list, items excluding postural tests can be combined. So, specialized UI easily provides the physiologist with a computer experiment (simulation) very similar to experiments provided on a natural animal organism. Each experiment has to be specially marked for a further independent analysis. Therefore, a special simulation passport is necessary. The passport contains the experiment's characteristic information namely, the model configuration, parameters of tests, experiment's duration, human body position, as well as data concerning actual characteristics of receptors' gains and thresholds.

Certainly, numerical characteristics of models do not cover the entire diapason of the regulator mechanism or possible values of test parameters. Initially, SMT should adequately simulate physiological responses only within certain boundaries that are verified in special investigations. I

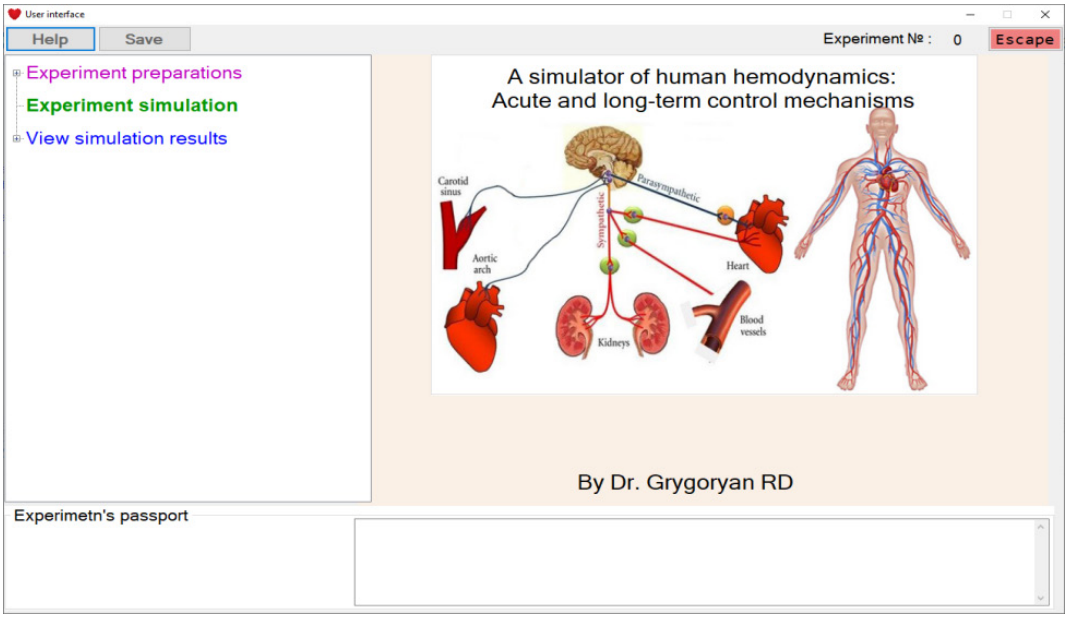

Figure 2. The face-list of SS.

shall note that there are not yet formal methods for the verification of every constant used in the model. Therefore, a big role played the 50-year experience in the creation of quantitative models of human physiology [12,13,15-17,39-43]. Additionally, to solve most problems, associated with both tuning and verification of models' constants, special software and interface were created [43]. That software provided access to about 450 parameters of models. But in the current software, only the most informative physiological characteristics are explicated in graph forms. Namely, the list of these characteristics includes those variables that physiologists usually try to observe and analyze in their traditional experiments. Seven groups collecting these characteristics are designed.

The first group consists of graphs representing dynamics of mean arterial pressure, systolic and diastolic arterial pressures in the aortic arch, the mean arterial pressures in the area of the carotid sinus, in the brain, kidneys, lungs, mean venous pressures in lungs veins, and in a central vein. Besides, the heart rate is also included in this group.

The second group is formed of graphs showing the dynamics of flows. Here are collected outputs of right and left ventricles, summary flow directed to the head and its separation to flows in hands and brain, flows into abdominal organs, kidneys, and legs.

The third group represents graphs of six sectional blood volumes. Body sections are associated with cavities and lungs. Such information is important for assessing the power of the regulators in different postures of a person.

The fourth group consists of graphs representing variables related to the chemoreceptor reflex. The group connects three input variables (pH, PaCO2, and PaO2) with afferent impulse patterns in the brain structures that, via modulating efferent sympathetic and parasympathetic impulse patterns, alter the lung ventilation, blood concentration of hemoglobin, as well as the state of CVS. The matter is that pH, PaCO2, and PaO2 depend on the total rate of energy consumption in cells.

The fifth group represents graphs of baroreceptor activities in four arterial zones: aortic arch, carotid sinus, Willis's circle, and lung artery.

The sixth group consists of graphs representing blood concentrations of glucose, glucagon, angiotensin-II, and the antidiuretic hormone.

The seventh group collects graphs representing characteristics of right and left ventricles.

6. Simulations Preparing and Execution

A general view of the main window of SS is shown in Figure 3. Namely, this window contains commands, necessary for both preparing and executing a simulation. In addition, the window also provides the user with the capabilities to look at simulation results.

Every simulation is an independent computer experiment with a previously collected configuration of models, chosen scenario, and observation duration. Operations needed to prepare and execute a computer simulation, as well as to analyze graph results, are listed in the left part of Figure 3.

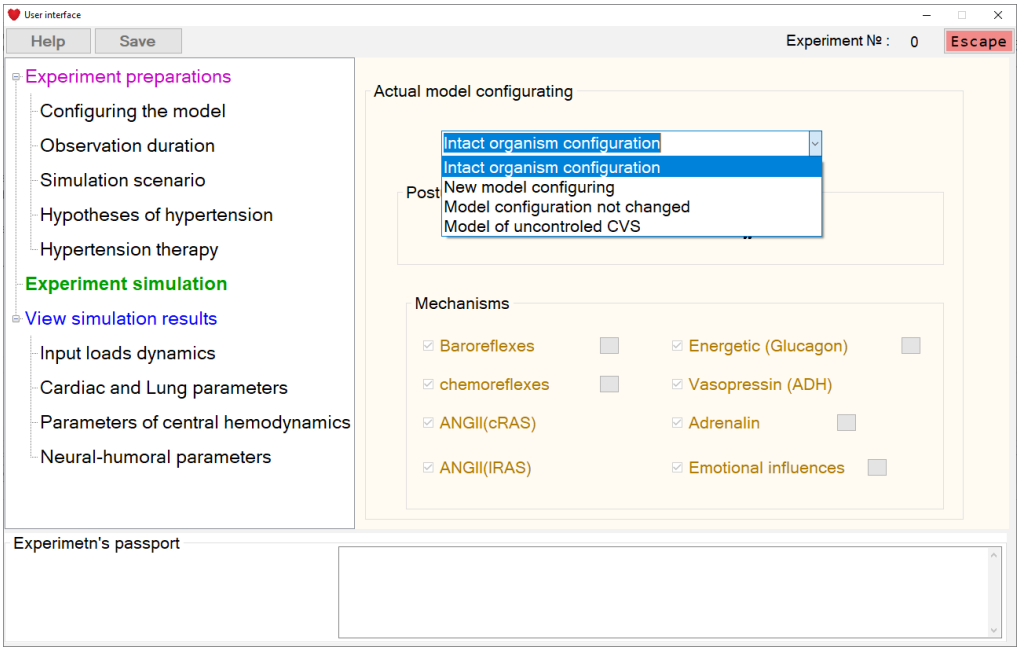

Figure 3. The look of the user interface in case of regulators' default (**Intact organism configuration**) or three other configurations. In cases the **New model configuring** is chosen, the field representing mechanisms is specific for each configuration. Specific case of **Model of uncontrolled CVS** suggests none regulator is active.

Model configuring is a multi-step procedure aimed to create the desired combination of active regulator mechanisms, tests to be applied, and simulation duration. Additional opportunities for model activation or deactivation are provided through the windows shown in the right sector of the main window. Some of these windows are pop-up windows. An example of the pop-up window designed to actualize the parameters of the simulation scenario is shown in Figure 4.

7. Several Test Results

The computer experiment starts when activated the position "Experiment simulation" and lasts until the Observation time (currently, it is 3 min.) is over. All simulation results are saved in the operative memory and can be called in form of graphs like those shown in Figure 6.

SS, supporting the creation of multiple versions of the basic model, is capable of providing the user with hemodynamic responses under different numbers of chosen input loads. In fact, these manipulations imitate empirical research with deactivation (activation) of certain control mechanisms.

8. Discussion

SS described in the paper is autonomous software based on a complex quantitative model and designed for providing experiments on IBM-compatible computers. At the same time, it is the first phase of the long-term fundamental investigation aimed to understand human integrative physiology by means of novel conceptual and methodological innovations. Innovations concern both concepts of circulation control and approach to mathematical modeling and roles of theoretical models in modern human physiological research. In particular, it is stressed that traditional empiric research has to be expanded with theoretical computer-based research. As the model contains equations and approximation constants that cannot be strongly validated, simulations of known tests are still the single way for arguing the adequateness of models. Namely, the paper was focused on this goal. However, it is worth noting that even during limited tests described in the paper, simulation results have not been entirely presented because of the paper's limited volume. At the same time, at this moment SS's thoroughly testing by physiologists has shown that the model reasonably imitates most cardiovascular responses to applied tests. Moreover, certain results of computer experiments, simulating arterial hypertension hypotheses also look rather reasonable. These arguments urge me that the simulation research concerning interactions of multiple controllers of circulation will really be interesting for traditional physiology and experts in areas of pathological physiology and medicine. I hope, a special publication on this subject, with proper citations of the current mathematical model, will be soon done.

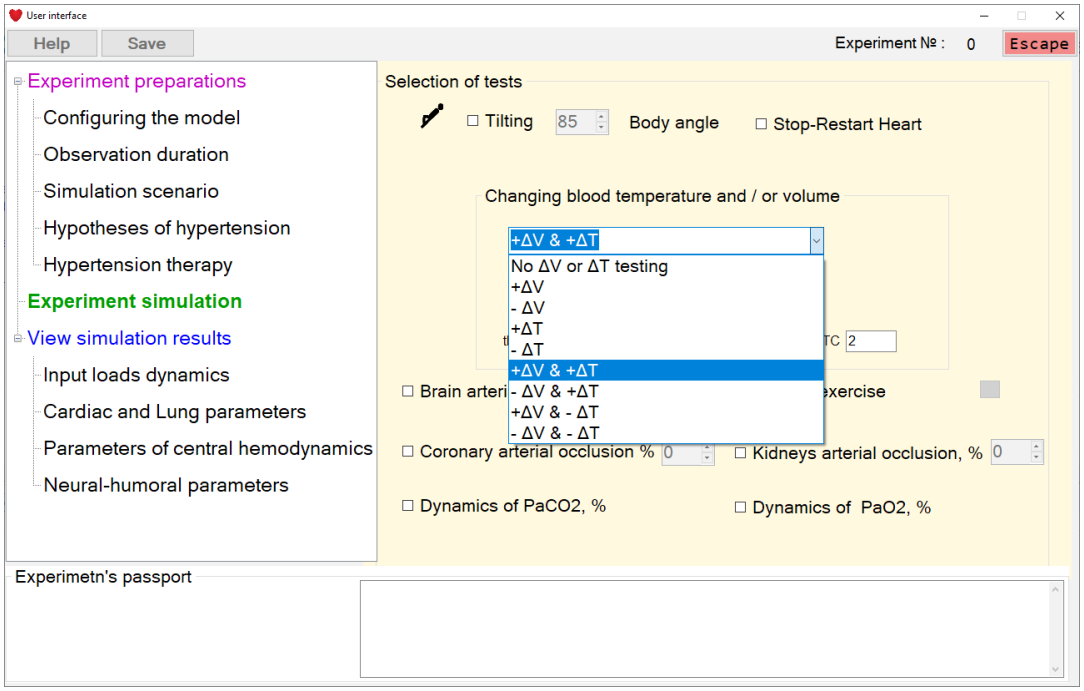

Figure 4. Preparing the simulation scenario.

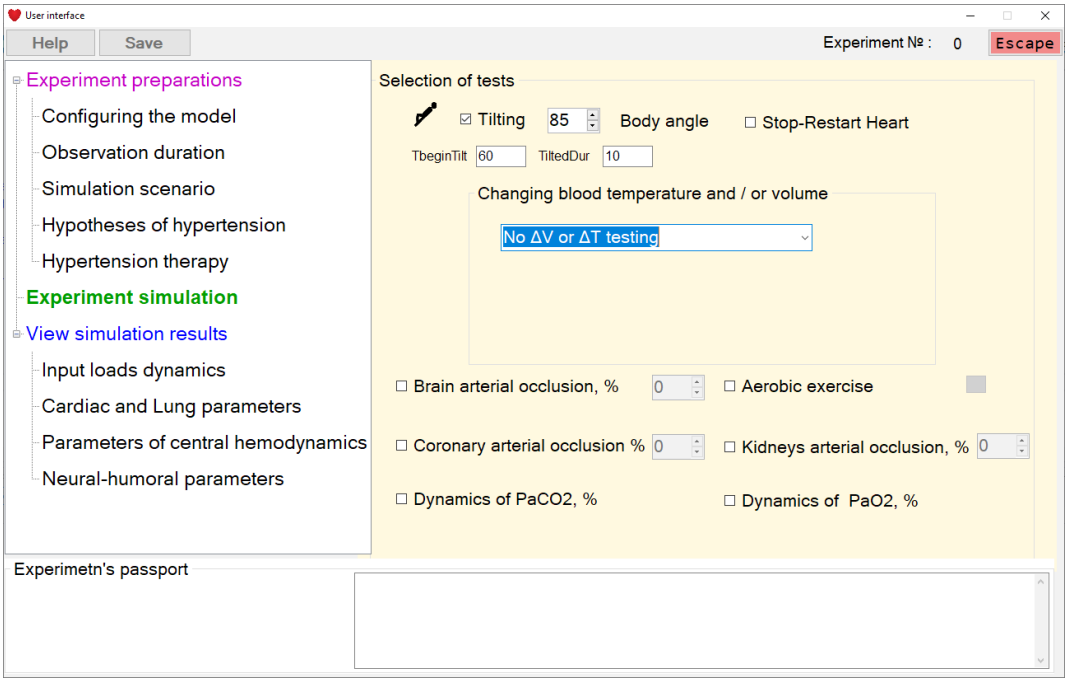

Figure 5. Preparing the simulation scenario (head-up tilting on 85° with T_T=10 sec.).

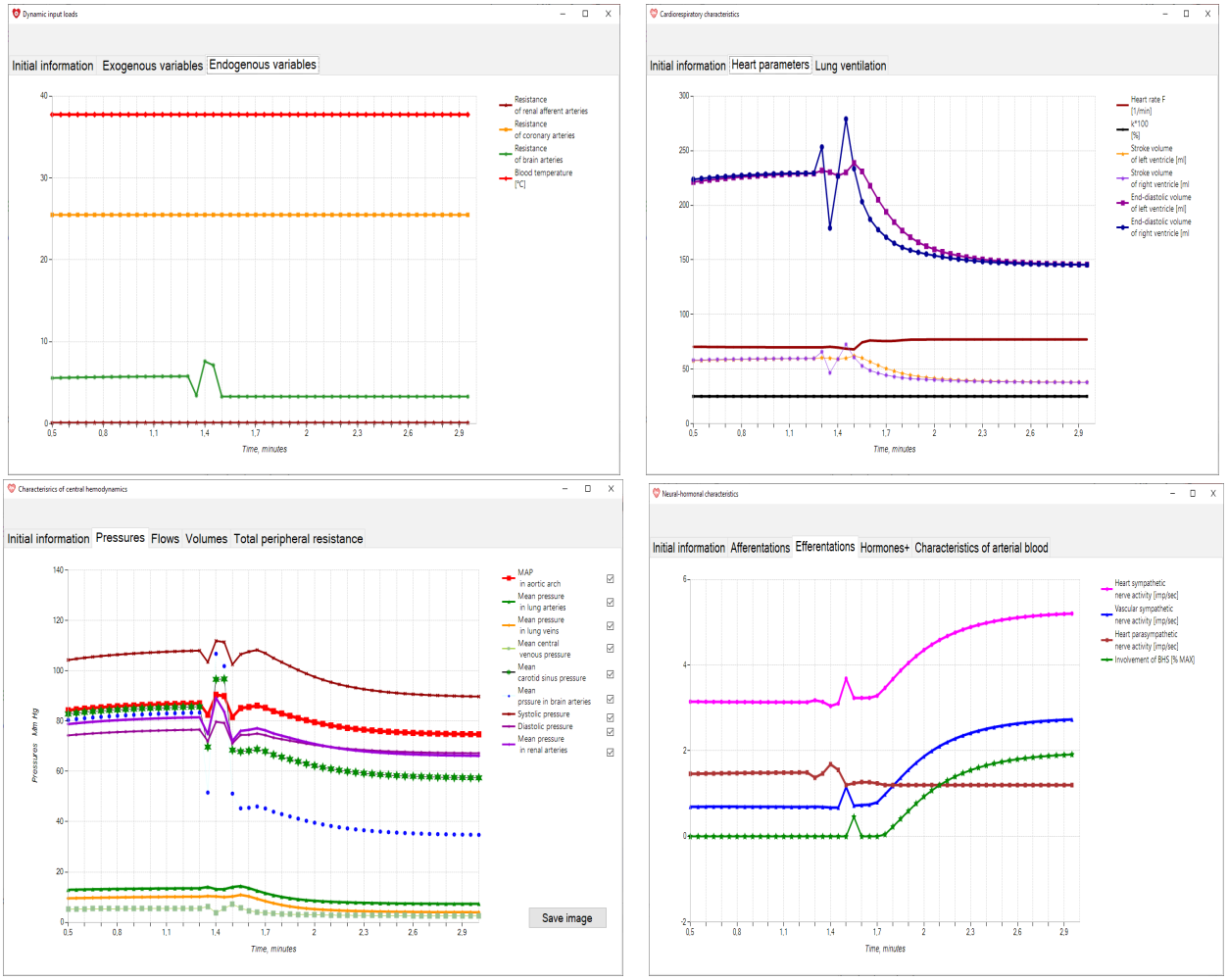

Figure 6. Several hemodynamic responses to the chosen simulation scenario (a 3-minute head-up tilting on 85° with T_T=10 sec.).

Figures 7-10 illustrate additional windows, containing special physiological data.

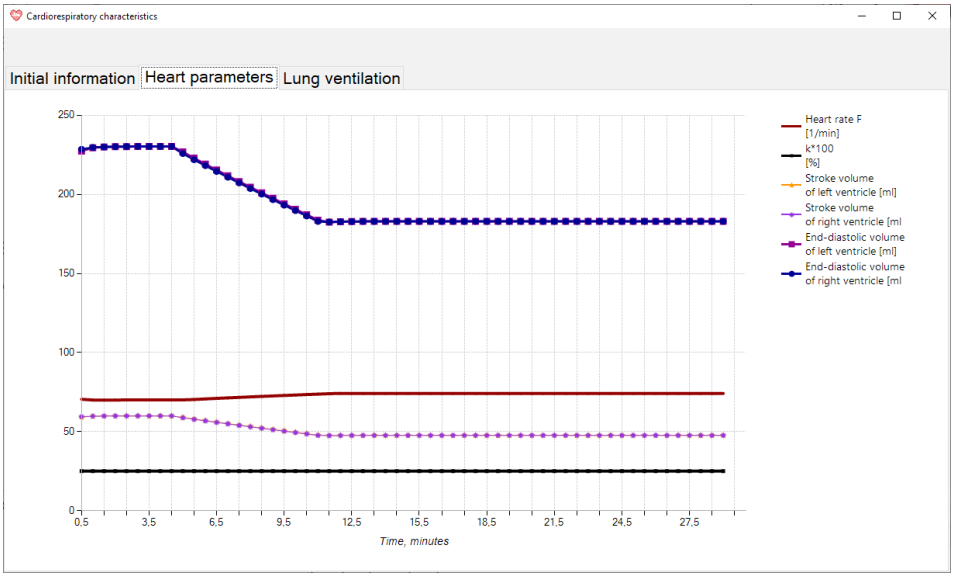

Figure 7. Heart responses to 500 mL venous blood lose started at 6-th minute of observation. Body position – horizontal.

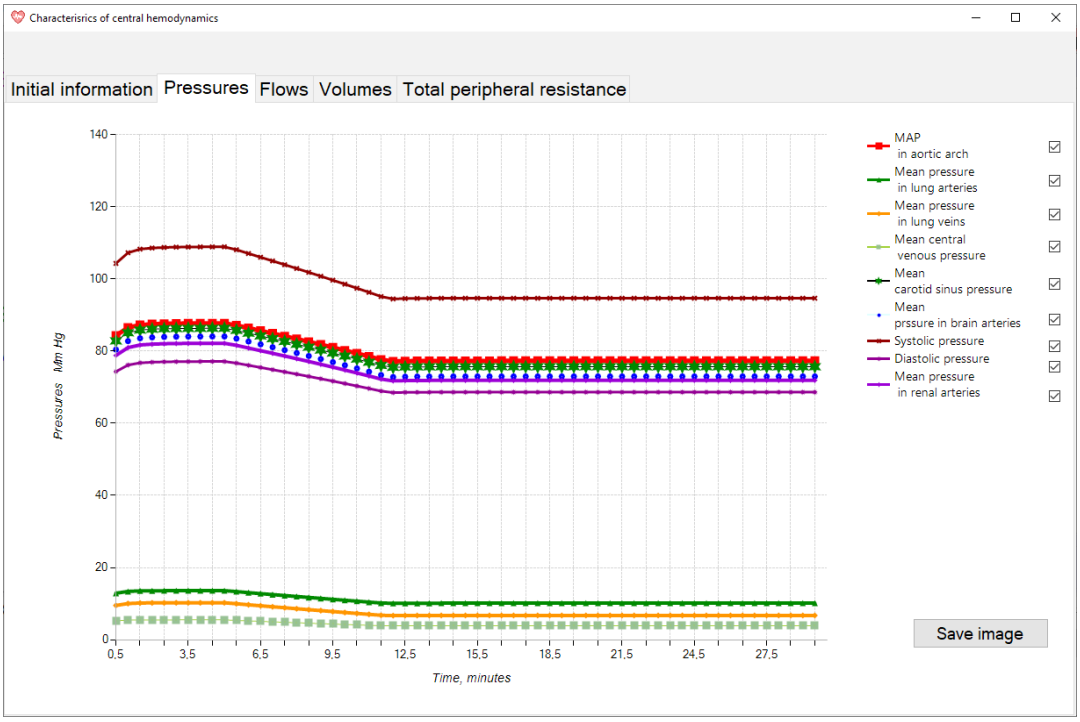

Figure 8. Pressures responses to 500 mL venous blood lose started at 6-th minute of observation. Body position – horizontal.

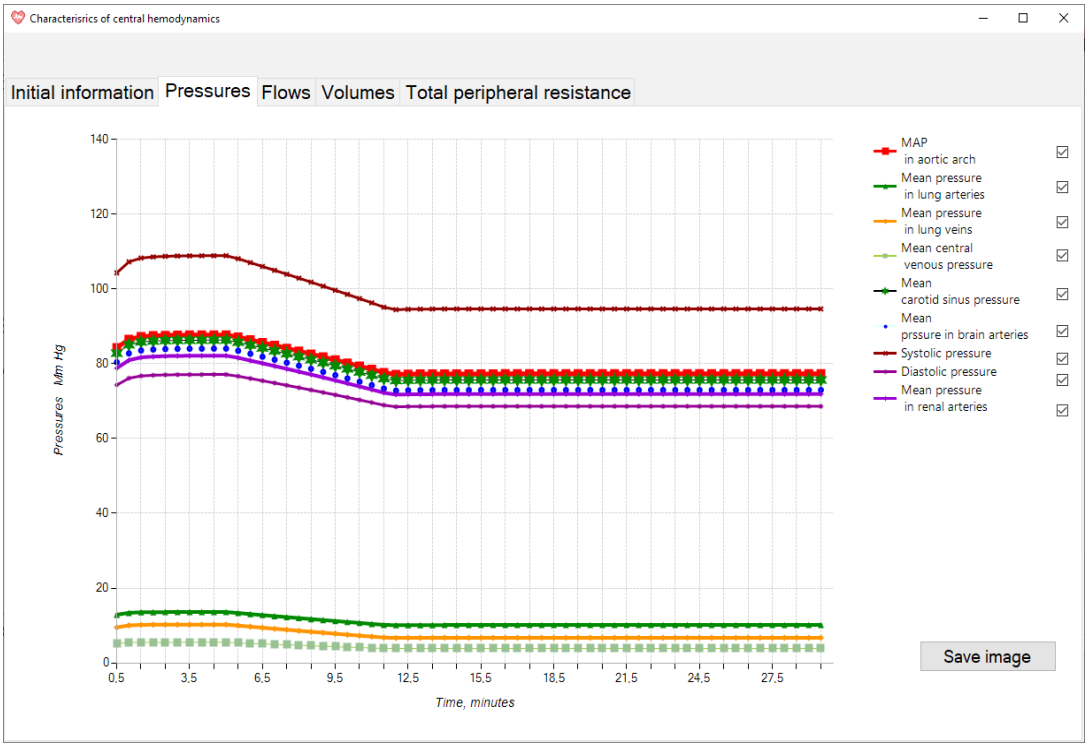

Figure 9. Volumes redistribution under 500 mL venous blood lose started at 6-th minute of observation. Body position – horizontal.

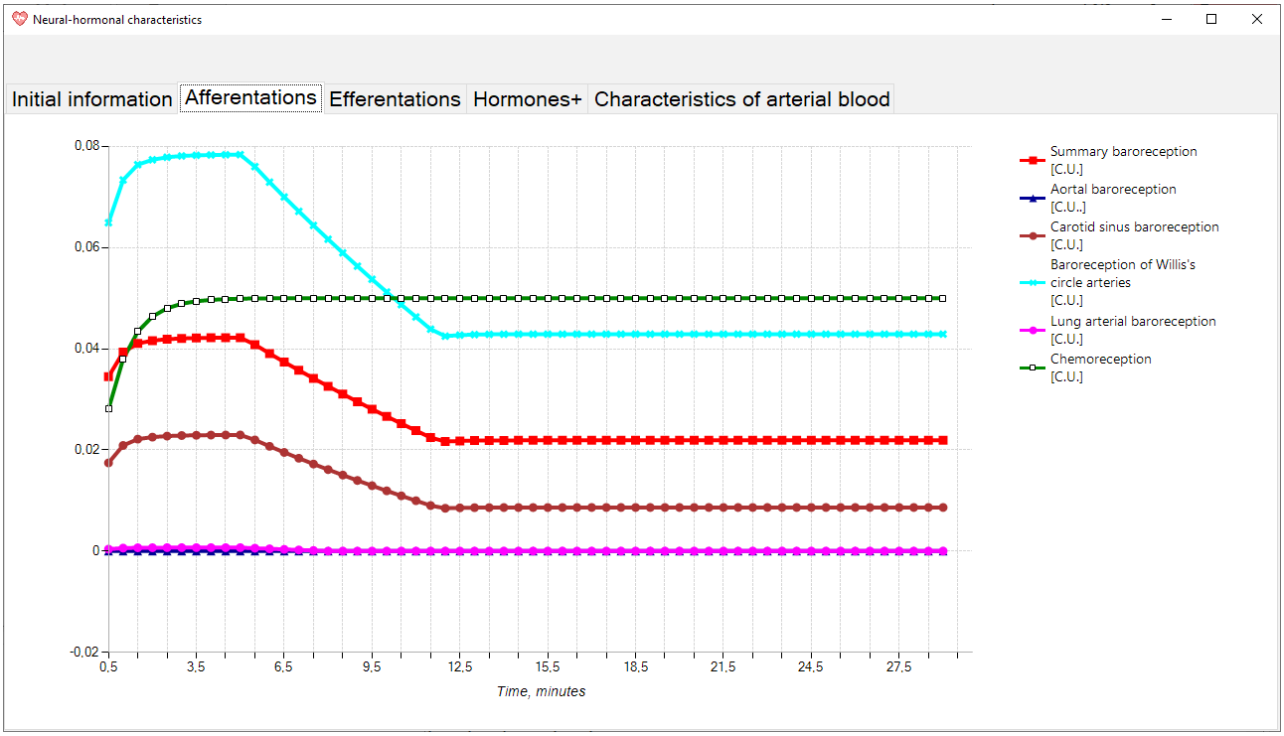

Figure 10. Changes of nerves' afferentation under 500 ml venous blood lose started at 6-th minute of observation. Body position – horizontal.

9. Conclusions

For the first time, a mathematical model and based on it special software (SS) capable of simulating alterations of human hemodynamics via automatic or arbitrary activations of main endogenous physiological mechanisms, are developed. Quantitative mathematical models represent CVS as an open system interacting with multiple associated organs and systems. Models have been tested and validated on the knowledge basis concerning the physiological norm. Additionally, the main hypotheses of arterial hypertension etiology can be modeled. SS provides physiologists with a novel research technology essentially widening and deepening the fundamental knowledge concerning human circulation. SS is also a good modern PC-based tool for simultaneous visualization of CVS's dynamic characteristics under the chosen list of input violations. The latter aspect will promote medical students to better understand non-obvious integrative human physiology and special pathologies. SS is also a good computer program to be used for educational purposes for illustrating main physiological and certain pathological regularities to medical students. We plan to expand the models and the software in order to simulate much more realistic scenarios of both normal and pathological human physiology.

The complex model includes 10 regulator-associated partial models. Even in the case when the test and its parameters are chosen, the user can provide experiments for 2^{10}=1024 combinations of activated or deactivated regulators. This number is too huge: in fact, no experimenter has ever explored the full range of regulators' combinations. Adding to this number also the versions that appear due to partial combining tests and modifying their parameters, one can see that the number of potential simulation scenarios becomes so big that can hardly be tested by creators of SS. At the same time, it is worth noting that the main constants of our models were tuned using specially developed assistant software [43]. These reasons give us a basis to consider our SS the first working version capable of essentially expanding the physiological research concerning mechanisms altering human hemodynamics. Further improvement of this SS needs proper feedback from physiologists exploring our SS. We are sure that the exploration will accumulate additional data requiring our more thorough analysis.

Acknowledgments

The author is thankful to Prof. V.F. Sagach who both consulted during user interface creation and organized the physiological testing of software. Special thanks to programmers O.I.Yurchak, A.G. Degoda, T.V. Lyudovyk, and T.V. Aksionova, who assisted during model testing.

Conflict of Interest

There is no conflict of interest.

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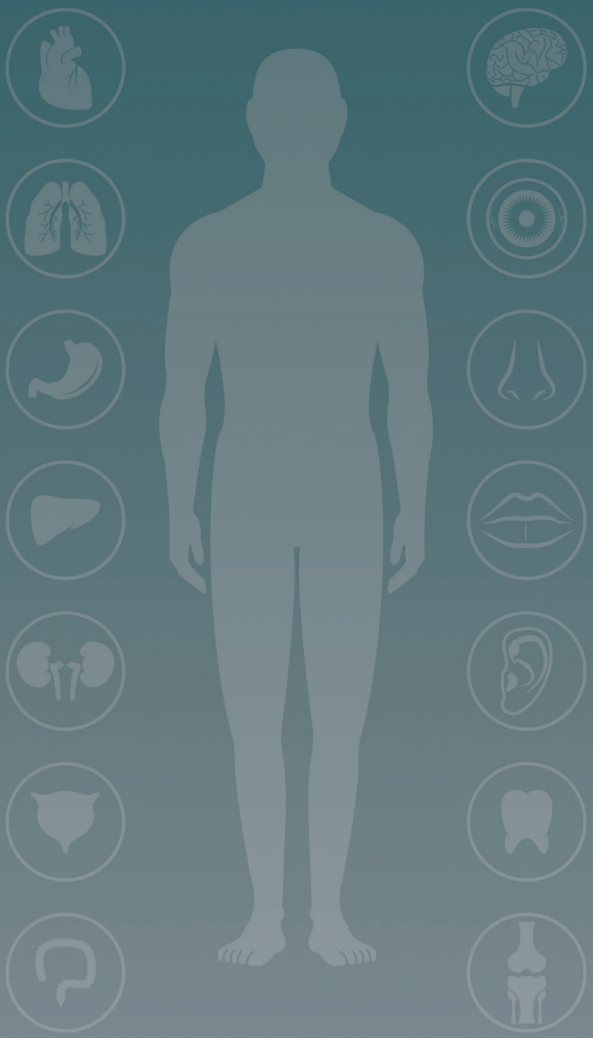

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