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SIMULATIONS OF HUMAN HEMODYNAMIC RESPONSES TO BLOOD TEMPERATURE AND VOLUME CHANGES

An advanced version (AV) of special software based on modified quantitative models of mechanisms that provide the overall control of human circulation is proposed. AV essentially expands the range of tasks concerning the modeling of cardiovascular physiology, in particular, the range of mechanisms controlling cardiac function, vascular hemodynamics, and total blood volume under unstable internal/external physiochemical environments. The models are verified on data representing hemodynamic responses to certain physical tests. In the publication, two test scenarios, namely blood temperature and volume dynamic alterations, have been simulated and analyzed in detail. The user-friendly interface provides all stages of preparation and analysis of computer simulation. The PC-based simulator can also be used for educational purposes.

Key words: physiology, cardiovascular system, hemorrhage, acute and long-term control, model, simulator

Introduction

Recently, we have proposed specialized software (SS) providing physiologists with additional research opportunities in the area of human cardiovascular system (CVS) [1,2]. Despite SS being previously tested and tuned for a mean healthy person, additional tests revealed certain quantitative inaccuracies. This forced us to critically analyze certain mathematical formalisms. As a result, a new version of SS, namely SS1, is developed.

This publication aims to illustrate both the correct models and their tests under certain simulation scenarios.

A short description of the basic model

SS is based on a complex quantitative mathematical model which presents the human CVS as an open system interacting with a certain number of associated physiological systems (APS). Within the framework of traditional physiology some of these APS are known as circulation controllers. They could influence the total blood volume dynamics and current values of CVS's parameters.

The core model and models of certain APS are described in [1] while models of modified APS are described in this paper. Structure of the complex model, necessary and sufficient for simulation of mechanisms controlling or modulating human hemodynamics under external/internal influences, was presented in [1].

Modified models of CVS controllers

Our models of cardiovascular control are based on concepts reflected in [3-6]. Several models are the advanced versions of the models proposed earlier [7-8].

Activities of efferent sympathetic ($E_S(t)$) and parasympathetic $E_V(t)$ nerves are under descending simulator ($E_{\delta}(t)$) or inhibitor ($E_{\delta}(t)$) influences of brain supra-bulbar neuronal structures. Simultaneously, ascending information 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 ($E_{\delta}(t)$) and parasympathetic ($E_{\delta}(t)$) heart nerves, as well as sympathetic vascular nerves ($E_{\delta}(t)$) are described as:

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

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

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

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

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

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

Here 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.

As the resistance depends on vascular volume, it is necessary to describe summary ($m1$) nervous-humoral alterations of volumetric characteristics.

$$D(t) = D0 + \sum_{i=1}^{m1} \Delta D_i(t);$$

$$U(t) = U0 - \sum_{i=1}^{m1} \Delta D_i(t),$$

where $D0, U0$ represent the initial values of $D(t)$ and $U(t)$.

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, $E_{\text{н}}(t)$, and $E_{\text{к}}(t)$. A special version of the model includes effects of exogenous cardio-active agents $C_a(t)$:

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

The 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 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 mean arterial pressure (MAP), can be considered to be constant only for very small values of the observation time τ. Modifiers of $V_S(t)$ are acting via changing the liquid intakes from the digestive system ($q_w(t)$), by means 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 $q_{cf}(t)$ are trans-capillary flows, $q_{es}(t)$ is the evaporation with sweat, $q_e(t)$ are expiratory fumes, $C_{bl}(t)$ are blood salt concentrations, $C_b(t)$ are concentrations of blood lipids. The remained notations in (*) represent approximation constants.

The initial value of total blood volume $V_S(t)$ is assumed to be $V(0)$. The model and simulation algorithms provide dynamic bide-side alterations of $V_S(t) = V(0) \pm \Delta V(t)$.

Vascular resistances $r_j(t)$, calculated as in [1,2], are changed 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 central renin-angiotensin system de-

scribes the dynamics of blood renin concentration $R_{nk}(t)$ in association with the critical value of pressure in kidney arterioles $P_{kc}(t)$ as:

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

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

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

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

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

$$R_{nT}(t) = R_{nk}(t) + R_{nh}(t) + R_{nl}(t) + R_{nL}(t) + R_{nb}(t)$$

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

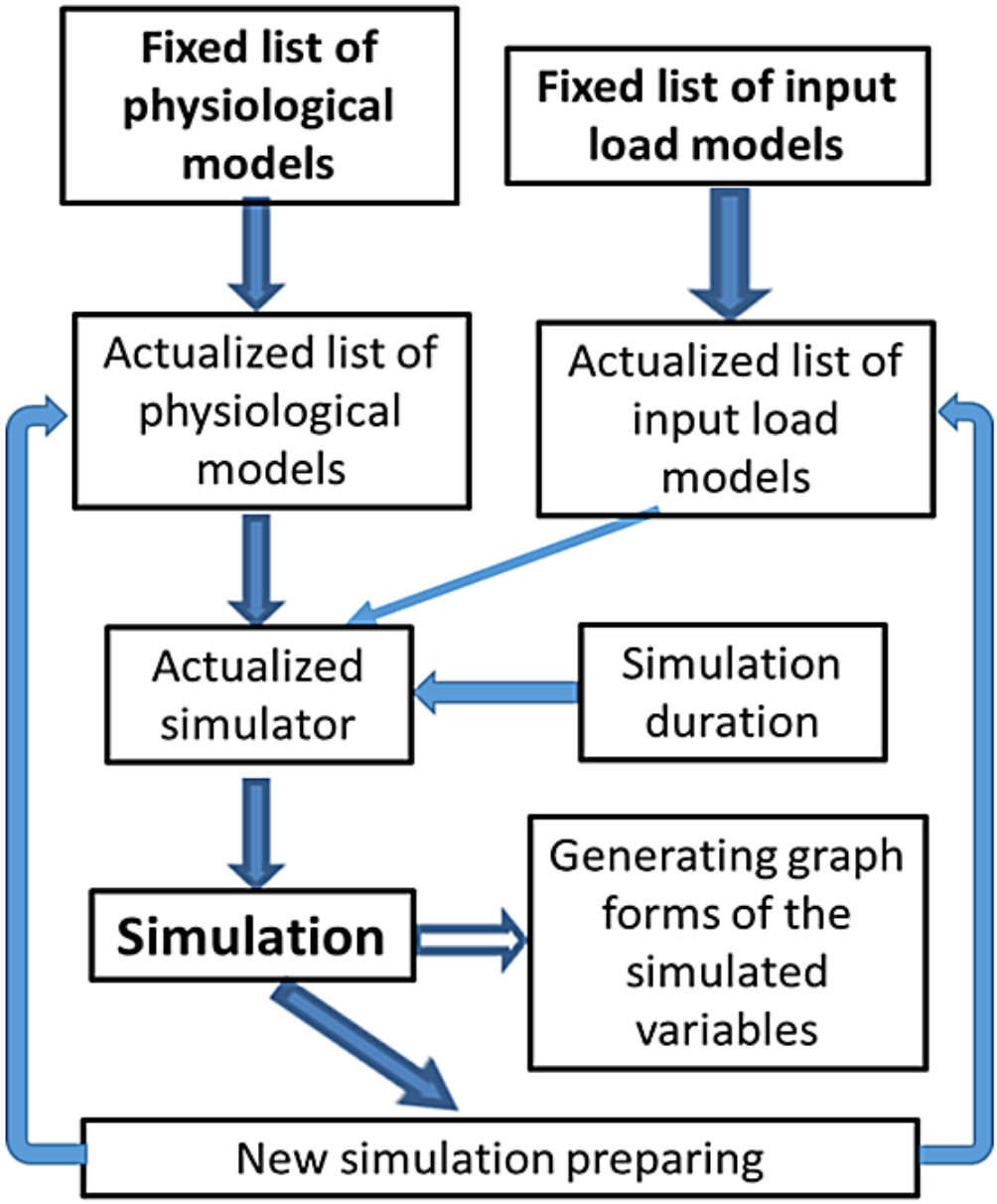

Fig. 1. Simulation algorithm.

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

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

Simulation algorithm

A single simulation algorithm (SA) depends on: 1) actual configuration of physiological models (ACPM); and 2) actual group of input loads (AGIL). This can be illustrated by means of Fig.1 which represents the general view on SA.

According to this algorithm, two independent procedures have to be performed before the simulator is ready to execute calculations. As a result of the first procedure the user gets the actualized ACPM. The second procedure generates AIGL. Additionally, the user has to set the simulation duration. Changing at least one value in characteristics of ACPM and/or AGIL, the user can start the next simulation.

Potentially, our simulator consists of 12 independently functioning physiological models and 10 models each representing one dynamic input load. So, the number of possible combinations of actualized ACPM and AGIL is too large. In fact, no empirical physiologist has ever observed hemodynamic effects of entire scenarios provided by our simulator. The user will be able to run and analyze the entire spectrum of simulations, he/she is provided by an effective user interface.

Input loads

Our models and the entire SS imitate dynamic physiological responses of a healthy person to dynamic input loads. Namely, a response depends on the absolute level and shape of the applied load. Theoretically, it is possible to create a simulator providing the construction of any arbitrary load profile. In this article, we consider only two input loads – alterations of blood temperature ($T^o(t)$) and total blood volume ($V_S(t)$)

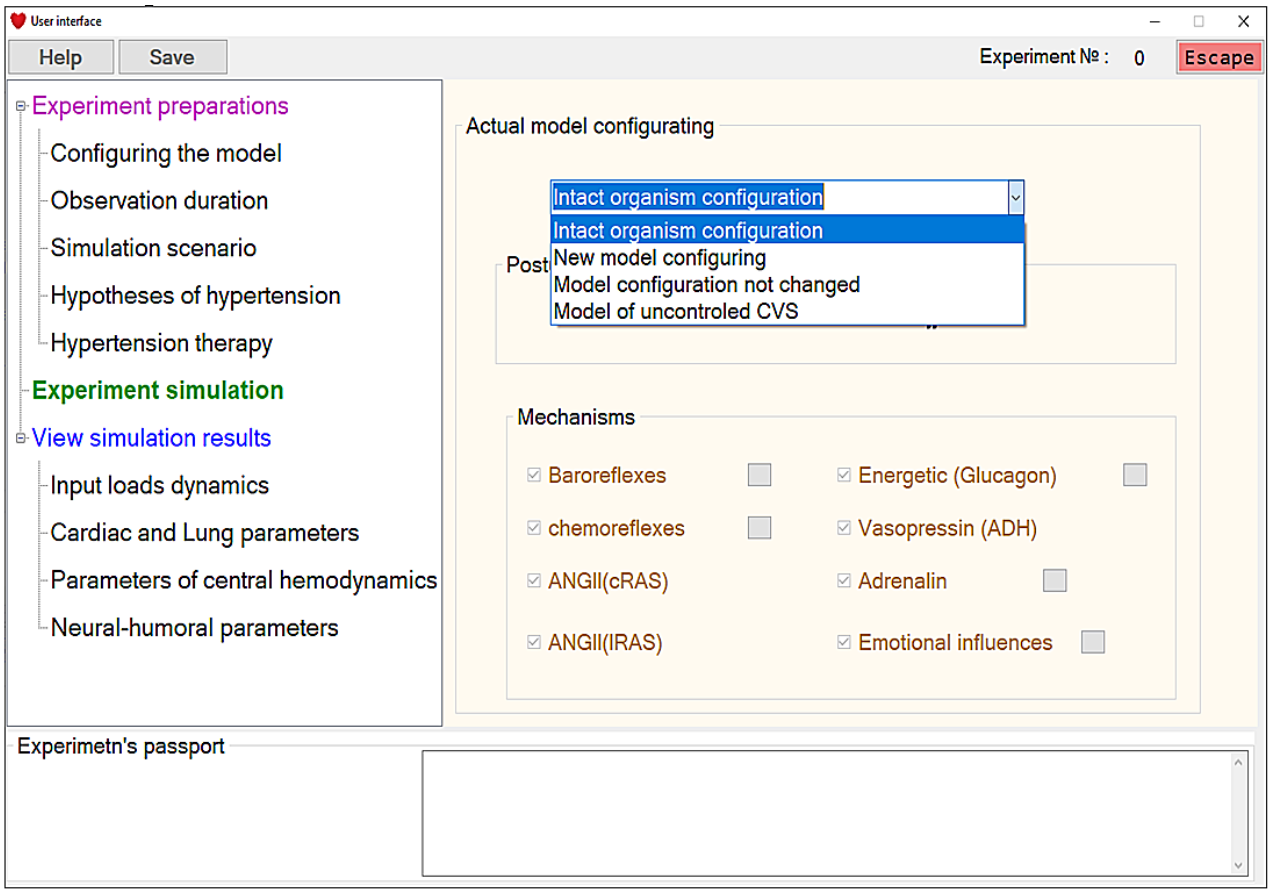

Fig. 2. User interface in case of regulators standard configuration (intact organism).

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

$$\Delta V(t) = \begin{cases} V_{ab}(t) \pm v_{al}; & T_{b\Delta V} < t < T_{b\Delta V} \pm \Delta V / v_{al} \\ V_{ab}(t); & t \le T_{b\Delta V}; t \ge T_{b\Delta V} \pm \Delta V \end{cases}$$

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

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 a user the 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 elevation ($+v_T$) until T_N^o reaches its maximal level ($T_{\max}^o$):

$$T^o(t) = \begin{cases} T_{\max}^o; & T^o(t) \ge T_{\max}^o \\ T_N^o + v_T \cdot t; & t_{bT} < t < t_{eT} \end{cases}$$

$$t_{eT} = (T_{\max}^o - T_N^o) / v_T$$

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

$$T^o(t) = \begin{cases} T_{\min}^o; & T^o(t) \le T_{\min}^o \\ T_N^o - v_T \cdot t; & t_{bT} < t < t_{eT} \end{cases}$$

$$t_{eT} = (T_N^o - T_{\min}^o) / v_T$$

Preparing computer experiments

As it was already mentioned in [1,2], each simulation is an independent computer experiment with a configuration of previously collected models. Opportunities for the forming of the actual model, experiment scenario, as well as for analyzing results in graph forms are presented in Fig. 2. This window is one of the main windows of the UI. The list of configurations is shown in the special pop-up window (see the middle-right part of Fig. 2). Operations needed to prepare every computer simulation and to provide its executing and results analysis, are listed in the window located on the left side of the UI. Information concerning details of every chosen string is indicated in the right side of the UI window.

Model configuring is a multi-step operation aimed to create the desired combination of activated regulator mechanisms, tests to be applied, and simulation duration. Additional opportunities for models 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.

Simulation (when activated) will last until the exposure time (observation duration) is over. All simulation results are saved in the operative memory thus this parameter of PC is critical for determining the maximal simulation duration.

Our simulator supports the creation of multiple biological model versions each of which is capable of providing hemodynamics under a single or several chosen input loads. In fact, these manipulations imitate empirical methods of certain control mechanisms deactivation (activation).

Main simulation results and discussion

The simulator described in the paper is autonomous software designed for IBM compatible computers. The simulator was designed as an alternative method and specialized research tool for theorization of human physiology. Its physiological basis includes almost all local or organism-scale physiological mechanisms capable to modulate the cardiovascular physiology under external/internal challenges. In fact, for the first time, our simulator does provide fundamental investigations aimed to understand human integrative physiology by means of conceptual and methodological renovations. A part of these renovations has been published [3-8]. The key conceptual renovation concerns the creation of opportunities expanding the sector of theoretical computer-based research. Basic models include both acute and long-term responses of the human cardiovascular system to a wide range of input physical alterations. Each such alteration causes specific physical (hemodynamic) alterations that

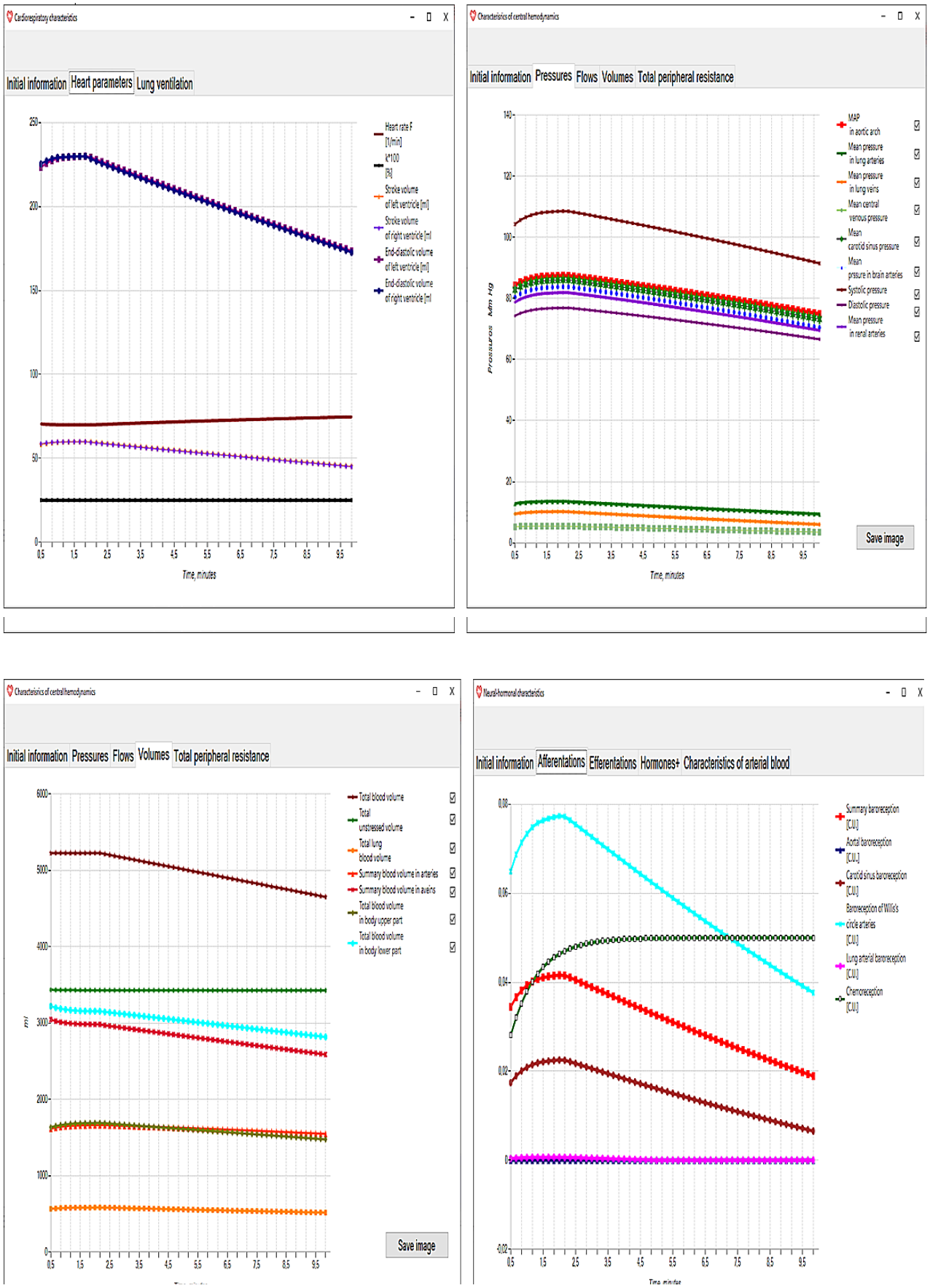

Fig. 3. Hemodynamic responses to hemorrhage of 1000 ml in human horizontal position.

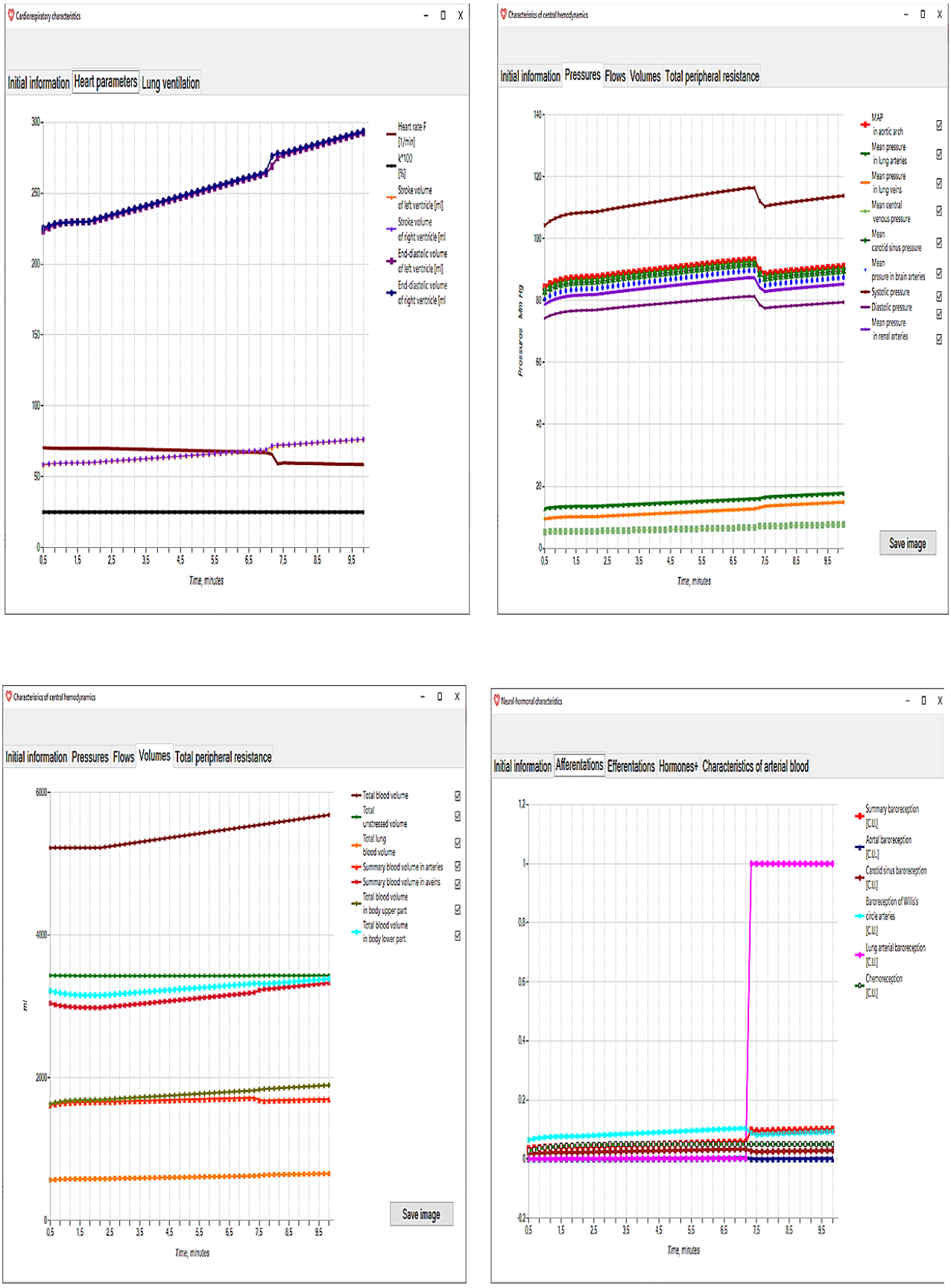

Fig. 4. Hemodynamic responses to blood infusion of 1000 ml in human horizontal position.

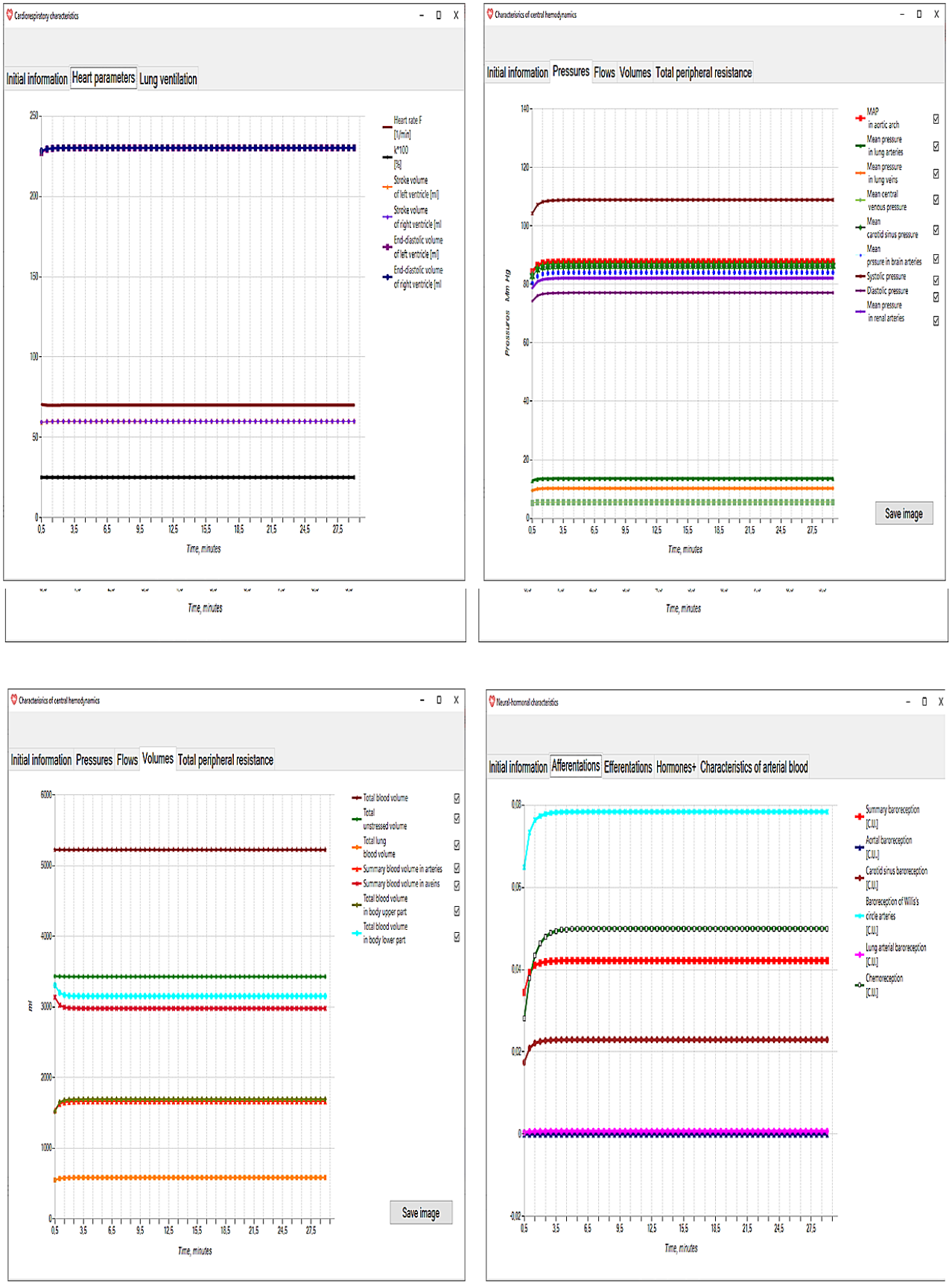

Fig. 5. Hemodynamic responses to blood temperature elevation in 3°C in human horizontal position.

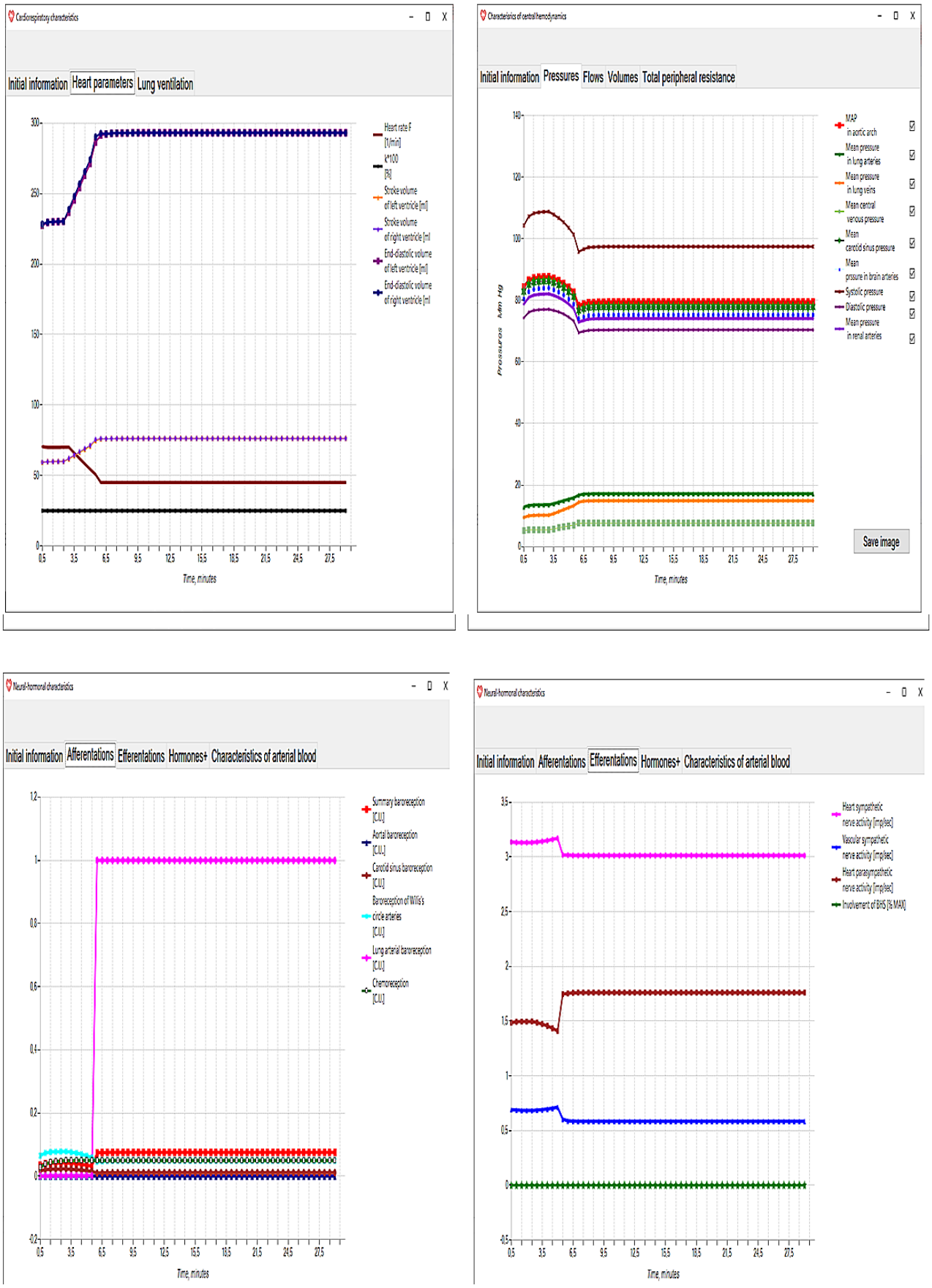

Fig. 6.Hemodynamic responses to blood temperature decrease in 3°C in human horizontal position.

in turn change the current mode of receptors associated with the nervous or humoral regulators. Their automatic response to these challenges normally provide certain changes in the heart pump function, in rigidities and unstressed volumes of vascular compartments, as well as in the total blood volume. In the frame of this publication, taking into account its limited volume, only alterations of two input variables are considered. The first one is total blood volume decrease (hemorrhage) or elevation by 1000 ml (main results are presented in Fig. 3 and Fig. 4 respectively). Results for the second variable, namely, the blood temperature change (decrease or elevation by 3°C) are presented in Fig. 5 and Fig. 6 respectively.

Illustrations in Fig. 3 - Fig. 6 reflect only a part of the data provided by the simulator. We have here chosen and presented mainly those physiological characteristics that either are reflected in appropriate empirical research or cannot be invasively measured in humans because of ethics. Unfortunately, we have no space for demonstrating analogous empirical graphs but we have used them during the models tuning [1, 6-8]. This statement concerns exclusively the case of alterations used for the total blood volume. The case of blood temperature dose elevation or decrease is not provided by proper empiric data because these data are still absent. Therefore, the role and the merit of simulations are exclusive. It is necessary to note that our models do not include central mechanisms of thermoregulation. All we have formalized concerns biophysics of cardiac pacemaker cells, that alter their frequency almost linearly with blood temperature changes. Another temperature target is smooth cells of arterioles. Their resistance is inversely related to local temperature. In case of further development, the central nervous control of activities in both effectors have to be added.

Conclusion

For the first time, special software (SS) capable of simulating alterations of human hemodynamics via automatic or arbitrary activations of main endogenous physiological mechanisms, is developed. SS is based on quantitative mathematical models representing CVS as an open system interacting with multiple associated organs and systems. Models have been tested and validated on the knowledge basis concerning physiological norm. Additionally, 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. Four simulation scenarios for the intact human model have been simulated. Two scenarios concern blood temperature dose both-side alterations, and two others concern total blood volume dose both-side alterations. Simulation results include the more comprehensive range of physiological information than conventionally provided in empirical studies. This is the main advantage of our SS. SS is also a good modern PC-based tool for simultaneously visualizing 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 in 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.

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