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Research Article

Model of human cardiovascular system with a loop of autonomic regulation of the mean arterial pressure

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Abstract

A model of human cardiovascular system is proposed which describes the main heart rhythm, the regulation of heart function and blood vessels by the autonomic nervous system, baroreflex, and the formation of arterial blood pressure. The model takes into account the impact of respiration on these processes. It is shown that taking into account nonlinearity and introducing the autonomous loop of mean arterial blood pressure in the form of self-oscillating time-delay system allow to obtain the model signals whose statistical and spectral characteristics are qualitatively and quantitatively similar to those for experimental signals. The proposed model demonstrates the phenomenon of synchronization of mean arterial pressure regulatory system by the signal of respiration with the basic period close to 10 seconds, which is observed in the physiological experiments. J Am Soc Hypertens 2016;10(3):235–243. © 2016 American Society of Hypertension. All rights reserved.

Keywords: Arterial pressure; autonomic regulation; baroreflex; cardiovascular system.

Introduction

The studies of complex multicomponent systems of the real world are usually accompanied by consistent improvement of the model. Starting with the simple block diagrams that only qualitatively describe the behavior of the real system, the models are developed and grow more complex as new knowledge becomes available. These more complicated models offer both qualitative and quantitative description of the observed phenomena. Simulation is of particular importance in physiology, biology, and medicine, where the possibilities of experimental invasive research and the range of acceptable impacts on the object under investigation are fundamentally limited.

The modeling of the human cardiovascular system (CVS) is one of the current problems in physiology. Physiological systems are usually complex and nonstationary. They are characterized by a network structure with a number of interacting elements. Currently, only few mathematical models of the CVS are known that take into account its autonomic regulation.[1–4] However, the necessity of modeling a large number of interacting functional elements in these articles has led to the simplification and linearization of the model description of such elements.

In particular, such reduction has resulted in modeling the system of baroreflex regulation of mean arterial pressure (AP) with the help of a first-order linear delay differential equation.[1–4] Such models of CVS regulation are unable to demonstrate stable self-sustained oscillations.[5] They exhibit only the regimes of forced oscillations under the influence of noise and other system elements impacting them. However, a number of researches point to an autonomous and self-oscillating nature of the system of mean AP

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baroreflex regulation based on the results of physiological experiments.[6–9] Similar conclusions were previously obtained in our experimental studies of regulatory system synchronization by respiration.[10–14]

Besides, on the basis of the results of in vitro studies in animals, the autonomous mathematical model for the system of baroreflex regulation of mean AP in mammals has been proposed in Ringwood and Malpas[15] in the form of a first-order nonlinear delay differential equation. The authors have shown that this model can demonstrate stable self-sustained oscillations with a characteristic period of about 10 seconds in humans.

In the present article, we propose a model of the CVS taking into account the nonlinear properties of the system of mean AP baroreflex regulation. The features of the proposed model are investigated by comparing the results of statistical and spectral analysis of the model heart rate variability (HRV) with the experimental data and a certain model proposed in Kotani et al,[4] which incorporates the systems of CVS regulation. Using the model and experimental signals, we investigate the phase synchronization of 0.1 Hz rhythms of mean AP baroreflex regulation system by respiration with the linearly changing frequency.

Material and Methods

Design of this study was approved by the Ethics Committee of the Saratov Research Institute of Cardiology (Saratov, Russia) in 2015.

Model of Cardiovascular System Autonomic Regulation

We propose a mathematical model of CVS which describes the main heart rhythm, the influence of autonomic nervous system on heart rate (HR), baroreflex regulation of mean AP, and formation of AP and takes into account the impact of respiration on these processes. The structure of the model is shown in Figure 1.

The proposed dynamical model includes four first-order differential equations:

$$\frac{d\varphi(t)}{dt} = \frac{1}{T_0} f_s(t) f_p(t), \tag{1}$$

$$\frac{dp_{dia}(t)}{dt} = -\frac{p_{dia}(t)}{R(t)C}, \tag{2}$$

$$\varepsilon \frac{d\overline{p}(t)}{dt} = -\overline{p}(t) + f(\overline{p}(t-\theta)) + k_1 B(t), \tag{3}$$

$$\frac{dc(t)}{dt} = -\frac{c(t)}{\varepsilon_c} + k_2 v_s(t-\theta_c). \tag{4}$$

The operation of heart sinoatrial node is described by Equation (1),[16] where $\varphi(t)$ is the phase of the heartbeat,

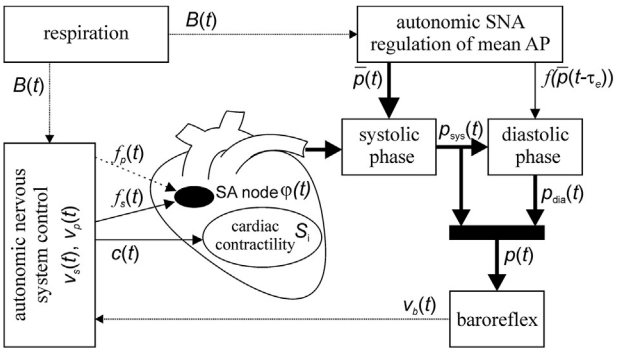

Figure 1. Schematic representation of the model. Impacts of vagus and sympathetic nervous activity (SNA) and AP are shown by dashed, solid, and bold lines, respectively. Other impacts are shown by dots. The activities of sinoatrial (SA) node and the system of mean arterial AP regulation are modeled too. AP, arterial pressure.

T_0=0.55 second is the period of denervated HR, and $f_s(t)$ and $f_p(t)$ are the influence of the sympathetic and parasympathetic divisions, respectively. In the absence of regulatory influences (denervation of the heart), f_s=f_p=1 and sinoatrial node generates periodic pulses with the period T_0. Under the influence of autonomic nervous system, the frequency of the HR is modulated and variability appears.

The dynamics of blood pressure in the systolic phase is modeled as:

$$p_s(t) = D_{i-1} + S(t)\frac{(t-T_{i-1})}{T_s}\exp\left(1-\frac{(t-T_{i-1})}{T_s}\right) + k_3\overline{p}(t) \tag{5}$$

where D_{i-1} is the magnitude of diastolic pressure at the end of the previous cardiac cycle, T_{i-1} is the duration of the previous cardiac cycle, $\overline{p}(t)$ is mean AP, and $S(t)$ is the cardiac contractility[3,4] expressed as follows:

$$S(t) = S'(t) + (S_a - S'(t))\frac{S'(t)^{n_1}}{S_a^{n_1} + S'(t)^{n_1}}, \tag{6}$$

where $S'(t)$=S_0+$k_4c(t)$+k_5T_{i-1} depends on the concentration of sympathetic agent noradrenalin (4) in the myocardium.[4]

In accordance with Seidel and Herzel,[3] $p_s(t)$ increases rapidly to a maximum value $p_s^{\max}$, which is reached after a fixed time T_s=0.125 second from the moment of the current heartbeat i used as a subscript of variables in the formulas. Blood pressure in the diastolic phase $p_d(t)$ relaxes from the maximal value achieved in systole phase $p_{d0}(t_i + T_s) = p_s^{\max}$ until the next heartbeat. This relaxation is described by windkessel effect caused by inertial properties of blood vessels (2). In Equation (2), C is a constant that determines the elasticity of the aorta and $R(t)$ is the

peripheral vascular resistance which depends on the mechanical properties of blood vessels R_0 and the arterial vasomotor tone, as follows:

$$R(t) = R_0(1 + k_6 f(\overline{p}(t - \theta_e))), \tag{7}$$

where R_0C=1.5 second, θ_e=3.24 second is the time lag of the signal propagation in the efferent nerves in the loop of baroreflex regulation of vasomotor tone of arteries, $\overline{p}(t)$ is the mean AP, and f is the nonlinear transfer function of sympathetic nucleus of central nervous system.

The AP $p(t)$ is the joining of the solutions of Equations (2) and (5) in the interval of current ith cardiac cycle:

$$p(t) = p_s(t), \;\; t_i \le t < t_i + T_s, \tag{8}$$

$$p(t) = p_d(t), \;\; t_i + T_s \le t < t_{i+1}. \tag{9}$$

To simulate the system of mean AP baroreflex regulation, we have rejected the linear conception developed in Seidel and Herzel[3] and Kotani et al[4] and in accordance with[15] used the Equation (3), where θ=θ_a+θ_e=3.6 seconds is the total time of the afferent (θ_a=0.36 second) and efferent (θ_e) delays in the loop of baroreflex regulation of arterial vessels tone, ε=2.0 seconds is the time constant of peripheral vessels, and $B(t)$ is the respiratory signal introduced in the equation according to Burgess et al.[5] In experiments with the fixed frequency of respiration, $B(t)$ was chosen as a harmonic signal:

$$B(t) = \sin(2\pi f_b t), \tag{10}$$

where f_b=0.29 Hz is the frequency of breathing. In experiments with the linearly increasing frequency of respiration, a harmonic signal with linear modulated frequency (linear chirp signal) was used as $B(t)$.

The nonlinear function f approximates the experimental transfer function of the nuclei of the central nervous system, governing the regulation circuit of the vasomotor tone. This function has the form:

$$f(x(t-\theta)) = G\left(\frac{r}{1 + e^{-\beta(x(t-\theta)-a)}} - \frac{r}{1 + e^{\beta(x(t-\theta)-a)}} + b\right) \tag{11}$$

and is presented in Figure 2.

Taking into account the nonlinear properties of the system results in Equation (3) describing an oscillator with time-delayed feedback, showing stable self-sustained oscillations with the frequency of about 0.1 Hz. Blood pressure is perceived by baroreceptors, and their response $v_b(t)$ is determined by AP value and its derivative according to the experimental results obtained in Warner[17]:

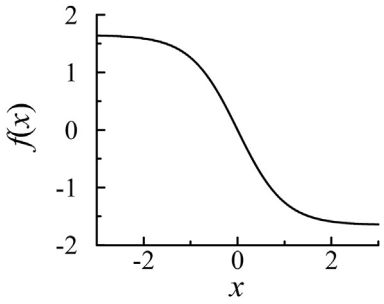

Figure 2. Nonlinear function f approximating the transfer function of the loop of baroreflex regulation of the vasomotor tone of arterial vessels. The parameters for f are chosen in accordance with Ringwood and Malpas.[15]

$$v_b(t) = k_7(p(t) - p_0) + k_8\frac{dp(t)}{dt} + \xi_1(t). \tag{12}$$

The nuclei of autonomic nervous system process the signals at the output of baroreceptors, providing activation of the sympathetic:

$$v_s(t) = \max(0, v_{s0} - k_9 v_b(t) + k_{10}|B(t)|) \tag{13}$$

and parasympathetic divisions of the autonomic nervous system[3,4]:

$$v_p(t) = \max\left(0, \;\; v_{p0} + k_{11} v_b(t) + k_{12}|B(t)| + \xi_2(t)\right). \tag{14}$$

The activity of autonomic nervous system is modulated by respiration $B(t)$ and is influenced by the normally distributed pink noise $\xi_2(t)$, which, as shown in Bunde et al,[18] has the central origin. The standard deviation of $\xi_2(t)$ is 0.1.

The effects of sympathetic and parasympathetic loops of baroreflex regulation on HR are expressed by the introduction of the sympathetic influence factor:

$$f_s(t) = 1 + k_{13}\left(c(t) + (c_a - c(t))\frac{c^{n_2}}{c_a^{n_2} + c^{n_2}}\right) \tag{15}$$

and the factor of parasympathetic influence[3,4]:

$$f_p(t) = 1 + k_{14}\left(v_p(t - \theta_p) + (v_{pa} - v_p(t - \theta_p))\frac{v_p^{n_3}(t - \theta_p)}{v_{pa}^{n_3} + v_p^2(t - \theta_p)}\right)F(\varphi(t)) \tag{16}$$

The sympathetic nervous system affects HR through a change in the concentration of noradrenalin (4). Its production is a relatively slow process (the characteristic relaxation time is ε_c=2.0 seconds) and is taken into account in Equation (4) by the delay time θ_c=1.65 seconds. The change in concentration of the parasympathetic system agent (acetylcholine) is much faster. This process is directly

taken into account in calculating $f_p(t)$ by the delay θ_c=0.5 second. The so-called curve of phase efficiency:

$$F(\varphi) = \varphi^{1.3}(\varphi - 0.45)\frac{(1-\varphi)^3}{0.008 + (1-\varphi)^3} \quad (17)$$

allows one to consider the impact of cardiac cycle phase on the operation of parasympathetic part of autonomic nervous system.[3]

Experimental Data

To verify our model for healthy subjects, we analyzed the HRV signals from 10 healthy men aged 20–25 years with no CVS abnormalities. To model the arterial hypertension (AH), we analyzed HRV signals from 10 untreated AH patients. The data were recorded from patients during their initial consultation before beginning of drug treatment. The results of nervous blockade modeling were compared with those presented in Jones et al.[19]

In our experiments with linearly increasing frequency of breathing, the subjects with no abnormalities of CVS were asked to inhale when the sound signal appeared. The signal frequency was linearly increasing from 0.05 to 0.25 Hz within 30 minutes. As well as in the case considered above, the respiration and electrocardiogram (ECG) signals were registered simultaneously, and afterward, the HRV signal was extracted from ECG.

In our study, we registered the experimental signals of respiration and ECG in I limb lead simultaneously. The signals were recorded in subjects lying down, at rest, two hours after the intake of food. The duration of each recording was 10 minutes. The HRV signals were obtained from the ECG signals.

Registration of Signals

All experimental signals were recorded using a standard device Electroencephalograph analyzer EEGA-21/26 "Encephalan-131-03" model 10 (Medicom MTD Ltd, Taganrog, Russia; URL: http://www.medicom-mtd.com/en/products/eega.html) with the sampling frequency of 250 samples per second and 14-bit quantization for each channel. We used silver chloride electrodes for ECG registration. To suppress a power-supply noise, we used a build-in notch filter. The bandwidth of the analog channel was 0.05–100 Hz.

Experimental Data Analysis

The following indices widely used in medical practice and physiological studies were calculated: The following indices widely used in medical practice and physiological studies and characterizing the low-frequency (LF) and high-frequency (HF) oscillations were calculated: LF—the mean spectral power calculated in the band 0.04–0.15 Hz, HF—the mean spectral power calculated in the band 0.15–0.4 Hz, LF/HF—the ratio of LF and HF, LF_{norm} and HF_{norm}—the ratio of LF and HF, respectively, to the power averaged in the band 0.04–0.4 Hz and the statistical characteristics of HRV including mean HR, RMSSD, and pNN50. The indices were calculated in accordance with the recommendations given in Berntson et al[20,21] and Appel et al,[22] using the original software developed by authors. Fourier power spectra were estimated by the Welch's method, using rectangular sliding windows with 120 seconds length and 60 seconds overlap.

To investigate the synchronization of complex oscillations, it is necessary to develop special methods for detecting the phase locking in the presence of dynamical and measurement noises. Another important task is the distinction of such nonlinear effect as phase locking from the so-called leakage, when an external signal is linearly mixed with the dynamics of the system. To solve this problem, we used the approach proposed in Hramov et al.[23,24] It is based on the analysis of instant phases of oscillations using continuous wavelet transform. It has been shown that within the region of synchronization of self-sustained oscillators by the signal with linearly varying frequency, the phase difference is linearly changed by π value. Otherwise, the mixing of self-sustained oscillations and external signal or combination of mixing and phase synchronization takes place.[23,24]

Results

Modeling of Healthy Subjects

Many studies[20–22] note that the spectral and statistical analysis of HRV helps to effectively evaluate the functional state of CVS regulatory systems. The calculation of indices characterizing the average oscillation power in different frequency bands, as well as the statistical characteristics

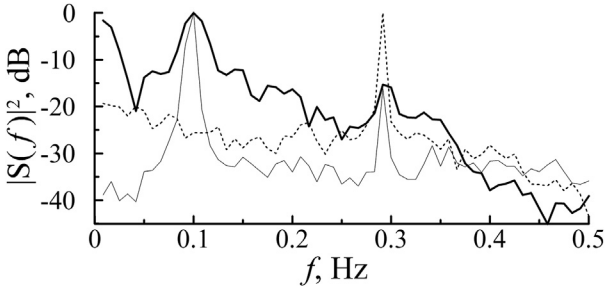

Figure 3. Power spectra of the experimental HRV of a healthy subject (bold line) and HRV simulated by the model M (thin solid line) and model K (dotted line). HRV, heart rate variability.

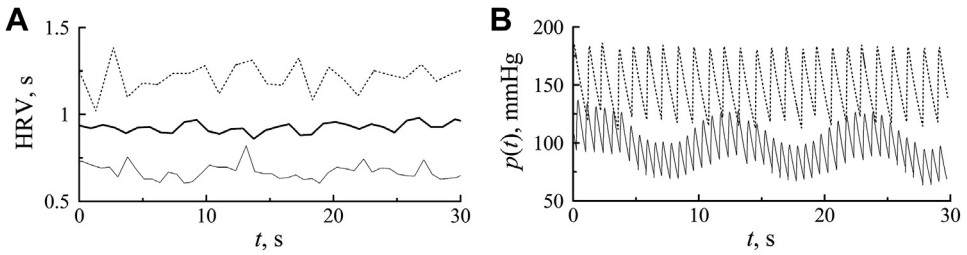

Figure 4. Time series of HRV (A) and AP (B). Experimental time series is shown with bold line, whereas the model time series are shown with thin solid line and dotted line for model M and model K, respectively. HRV, heart rate variability.

of HRV, is widely used in physiological research and medical diagnostics.

A typical Fourier power spectrum of HRV signal for a healthy subject estimated by Welch method for a 10-minute experimental realization is presented in Figure 3 by a bold line. It was compared with the power spectra of HRV signals generated by the model by Kotani et al[4] (hereafter, for short, we will denote it as ''model K'') and our model (denoted as ''model M'').

Because the self-sustained oscillations in the loop of arterial vessel tone regulation have been taken into account in model M, we have been able to tune the power of spectral components and to align them accurately with the experimental results. Compared to model M, the component at a frequency of about 0.1 Hz, which reflects the activity of the sympathetic part of autonomic regulation of the CVS, is not expressed in the HRV spectrum of model K with the original parameters corresponding to healthy subjects at rest.

The time series of experimental and model HRV and simulated AP are presented in Figure 4. Systolic and diastolic pressures are in the ratio 200/110 for model K and 145/70 for model M. The latter ratio better reflects typical values for healthy subjects at rest.

The spectral and statistical indices calculated from the experimental signals of HRV were compared with those calculated from the simulated time series. For this purpose, an ensemble of 10 realizations was generated from each model. The length of these simulated realizations was the same as for experimental records. The estimated indices are presented in Table 1. One can see that the values of indices calculated for model M are closer to typical experimental values than the values of indices calculated for model K.

Modeling of AH

We have carried out modeling of AH. For that purpose, we used the model's coefficients listed in Table 2. We compared the averaged indices calculated from 10 realizations of the proposed model with those calculated from the data acquired from 10 AH patients (see Table 3). As it can be seen from Table 3, the model M is able to reproduce the averaged statistical and spectral indices typical for AH patients.

Modeling of Autonomic Blockade

The modeling of autonomic blockade is an important and interesting problem. Deeper understanding of the CVS functioning could be achieved by studying the processes that take place during lesions of the autonomic nervous system or during pharmacological autonomic blockade. This problem was experimentally studied in a number of articles.[19,25] We modeled the CVS of healthy young men before autonomic blockade using a set of coefficients listed in Table 2. To model the established autonomic blockade the following parameters were set to 0: k_2, k_3, k_4, k_6, k_{12}, and k_{13}. The results of our numerical experiments were compared with the results presented in Jones et al.[19]

Figure 5 shows the changes caused by autonomic blockade in systolic blood pressure, diastolic blood pressure, HR, and stroke volume. The changes were calculated for 26 realizations of the model and then averaged. The obtained results agree well with the results reported by Jones et al.[19]

Diagnostics of Phase Synchronization

The indices estimated in the course of the spectral analysis of HRV have demonstrated their informational content and importance in medical diagnostics. However, the linear

Table 1
Indices averaged over the ensemble and the errors of the mean for models and healthy subjects data

Indices	Experiment	Model M	Model K
HR, beats/min	74.6 ± 2.9	89.7 ± 0.0	46.6 ± 0.0
RMSSD, ms	46.8 ± 5.9	52.4 ± 1.2	122 ± 1.6
pNN50	26.9 ± 5.6	29.7 ± 0.8	71.0 ± 0.9
LF, ms^2	549 ± 69	607 ± 15	228 ± 12
HF, ms^2	543 ± 110	249 ± 11	1719 ± 44
LF/HF	1.92 ± 0.37	2.47 ± 0.17	0.13 ± 0.0
LF_{norm}	40.1 ± 4.5	69.4 ± 2.5	11.4 ± 0.9
HF_{norm}	30.4 ± 4.1	29.2 ± 2.2	66.8 ± 0.8

HR, heart rate.

Table 2
Indices averaged over the ensemble and the errors of the mean for modeling the AH and 10 AH patients

Parameter	Healthy Patient	Arterial Hypertension	Autonomous Blockade
T_0, s	0.55	0.7	0.7
S_0, mmHg	25	18	18
S_a, mmHg	35	70	70
n_1	3	2.5	2.5
k_4, mmHg	40	40	40
k_5, 1/mmHg	10	15	15
T_s, s	0.125	0.125	0.125
k_3, mmHg	3	0.7	2.5
R_oC, s	1.5	1.3	1.3
k_6	0.015	0.015	0.015
θ_e, s	3.24	3.24	3.24
ε	2.0	2.0	2.0
θ, s	3.6	3.6	3.6
k_1	2.5	2	2.5
f_b, 1/s	0.29	0.29	0.29
G	1.65	1.65	1.65
r	2	2	2
α	1	1	1
β	2	2	2
a	0.5	0.5	0.5
b	0	−1.5	−1.5
k_7, 1/mmHg	0.02	0.02	0.02
k_8, s/mmHg	0.00125	0.00125	0.00125
p_0, mmHg	50	50	40
ν_{s0}	0.8	2.8	1.8
k_9	0.7	0.6	0.6
k_{10}	0.025	0.02	0.025
ν_{p0}	0.0	0.3	0.3
k_{11}	0.3	0.3	0.3
k_{12}	0.025	0.02	0.025
std $\xi_1(t)$	0	0.015	0.12
std $\xi_2(t)$	0.1	0.02	0.1
k_{13}	1.6	0.3	0.3
c_a	2.0	2.0	2.0
k_{14}	5.8	5	5.8
θ_p, s	0.5	0.5	0.5
ν_{pa}	2.5	2.5	2.5
n_2, n_3	2.0	2.0	2.0
ε_c, s	2.0	2.0	2.0
k_2	1.2	0.15	0.15
θ_c, s	1.65	1.65	1.65

spectral estimates do not provide information about the features of complex nonlinear collective dynamics of interacting regulatory systems. This can be explained by the complexity of signals under research. Their detailed analysis requires the development of specialized nonlinear methods. Previously, we have experimentally shown that the regulatory systems with the basic frequency of about 0.1 Hz exhibit complex regimes of collective dynamics

Table 3
Indices averaged over the ensemble and the errors of the mean for modeling the AH and 10 AH patients

Indices	Experiment	Model M for AH
Systolic pressure, mm Hg	156 ± 6.2	153 ± 0.02
Diastolic pressure, mm Hg	95 ± 9	93.3 ± 0.02
HR, beats/min	70.2 ± 6.09	76.4 ± 0.02
LF, ms^2	92 ± 40.4	111 ± 4.44
HF, ms^2	118 ± 92	116 ± 5.8
LF/HF	1.73 ± 1.11	0.96 ± 0.05
LF_{norm}	30 ± 10.1	48.8 ± 1.43
HF_{norm}	26 ± 15	51 ± 1.43

HR, heart rate.

and can demonstrate the phase and frequency synchronization between themselves.[10,11]

We have shown the importance of these results for medical diagnostics.[12,13] In addition, it was shown that the systems of regulation are synchronized by the signal of respiration with linear chirp signal. Such behavior is typical for self-sustained oscillators of any nature.[14] In the present article, we examine how the models behave under the influence of respiration with linearly varying frequency.

Figure 6 shows a typical phase difference between the analyzed signals that was calculated from experimental and simulated data. As it can be seen from Figure 6 , the linear section of the phase difference is varied by π value indicating the presence of phase locking for the experimental signals and model M signals. Moreover, the intervals of phase locking for model M and experimental signals are similar. The phase difference for model K does not show a linear variation by π value, and as a result, the phase synchronization is not observed in this model. Only the effect of mixing is observed in model K. In our studies, model K parameters were varied in a wide range. In particular, the respiration impact (coupling strength coefficient estimated with respect to standard deviation of the autonomous system signal) was increased up to 20 times in comparison with model M, but no signs of the phase synchronization were observed.

Discussion

The development of mathematical models of biological systems is an important step in studying the living systems. Such models can provide fundamentally important information on the system structure and interaction between its elements, they can describe biological systems both quantitatively and qualitatively. They allow one to investigate the system behavior in time and under parameter variation and predict the effect of physiological tests and medical drugs on the system.

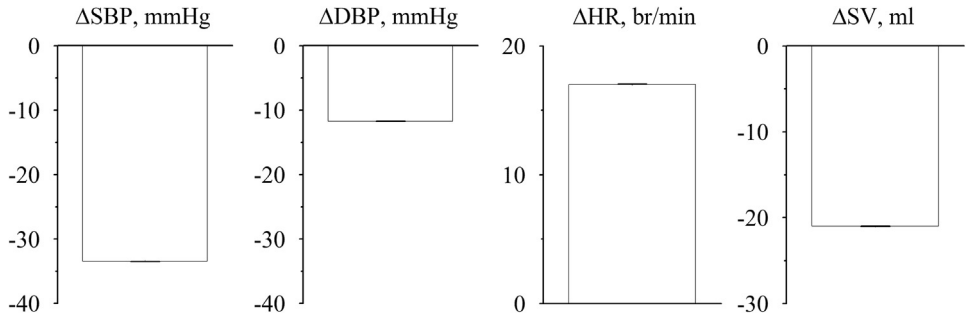

Figure 5. Change of indices in healthy young men during the blockade modeling. DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; SV, stroke volume.

Modeling complex multicomponent biological systems generally requires the use of cumbersome high-dimensional equations. Therefore, model reduction is often resorted to simplify the task. In particular, it is limited to linear representations of the structure of some functional system elements. However, taking into account the nonlinear properties of the simulated systems in accordance with the relevant physiological representation enables us to qualitatively change the model behavior and quantitatively describe the effects observed in the experiments. Moreover, a number of these effects cannot be modeled within linear approximations.

Here, we have examined the mathematical model K proposed in Kotani et al[4] because currently this model can give the most detailed description of the CVS activity regulation. However, the linear description of the mean AP regulation loop used in this model limits its capabilities.

In particular, the system of baroreflex regulation of arterial vasomotor tone is described in model K by the linear equation with time delay. Therefore, the simulation of the characteristic peak in HRV power spectrum at a frequency of about 0.1 Hz reflecting the sympathetic nervous activity in the experimental data is possible only in the case of exciting passive systems by dynamical noise and external signals. The appearance of the peak at 0.1 Hz in the power spectrum of this model is caused by resonance properties of the system and the amplitude-frequency characteristics of linear system.

We have proposed a mathematical model with the structure close to that of model K. However, the qualitative distinction of our model from model K is in using nonlinear self-sustained time-delay system for simulation of mean AP baroreflex regulation similarly to the model proposed in Ringwood and Malpas[15] on the basis of in vitro experiments on animals. The introduction of the autonomous self-sustained element in the proposed model has greatly improved simulation of the spectral properties of the experimental data and statistical indices characterizing HRV properties. Moreover, the proposed model qualitatively and quantitatively simulates the effect of phase synchronization of the dynamics of the loop of mean AP baroreflex regulation by the signal of respiration with linearly changing frequency. This was impossible to achieve with the help of model K because its elements are linear.

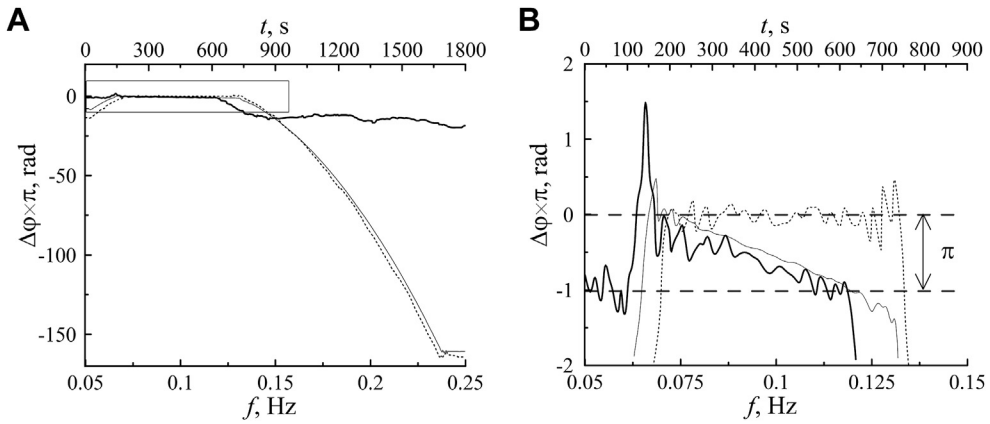

Figure 6. (A) Differences of instantaneous phases of 0.1 Hz oscillations in the system of mean AP regulation and the driving signal $B(t)$ with the linearly increasing frequency f_r. (B) Enlarged fragment of (A). Experimental phase difference is shown with bold line, while the model phase differences are shown with thin solid line and dotted line for Model M and Model K, respectively. AP, arterial pressure.

It is shown that by varying the coefficients of the proposed model, it is possible to reproduce the statistical and spectral indices typical for patients with AH and with autonomic blockade. The physiological interpretation of the obtained coefficients is a subject of further research.

We believe that our results support the hypothesis of a high autonomy of baroreflex regulation loop of mean AP. The obtained results demonstrate the importance of considering the nonlinear properties of the regulatory systems in their mathematical modeling and point to the fundamental significance of nonlinearity in the operation of physiological systems.

Conclusion

We proposed a model of the human CVS. Its capabilities and the boundaries of applicability were compared with the experimental results and the model proposed earlier by Kotani. For this purpose, spectral analysis of HRV signals was carried out. In addition, frequency synchronization between 0.1 Hz oscillations in HRV signals and respiration with linearly changing frequency was detected.

It was shown that the addition of baroreflex regulation loop of mean AP in the form of self-sustained oscillator with time delay in the proposed model allows one to reproduce the power spectra, the values of statistical indices of HRV, and the ratio of systolic and diastolic blood pressure typical for healthy subjects at rest. Besides, the proposed model demonstrated the ability to simulate the phenomenon of phase synchronization of 0.1 Hz rhythm of mean AP baroreflex regulation and respiration with linearly changing frequency that was previously observed in our experiments. Moreover, it is possible to reproduce the autonomous blockade and AH by the choice of the model parameter values.

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